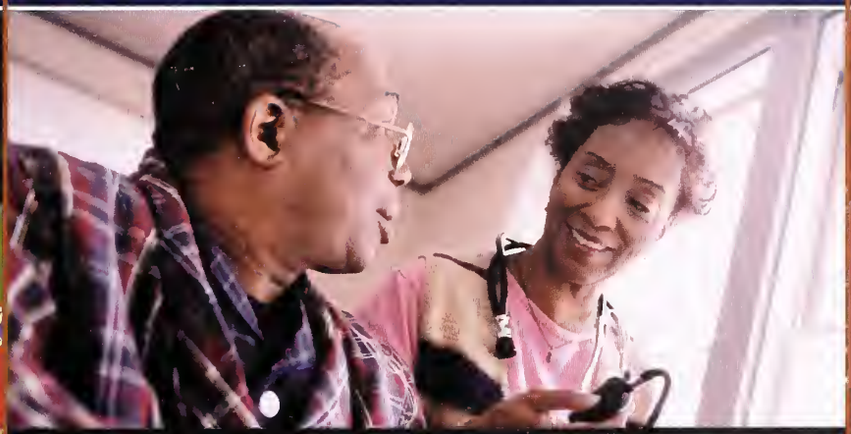
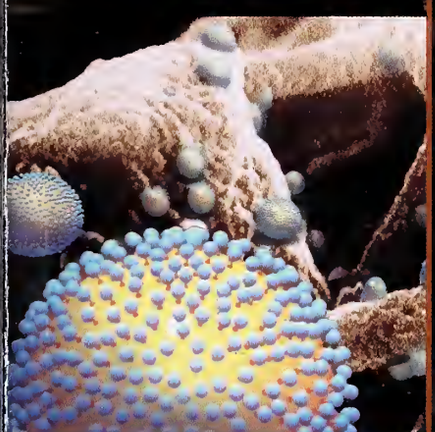
U.S. Department of Health and Human Services
National Institutes of Health



NIH

THE NATION'S MEDICAL RESEARCH AGENCY

Overview of Research Activities



The past few years have been a historic time for the National Institutes of Health (NIH) and for medical research in America. In 2003, we completed the doubling of the research budget at the NIH, expanding the hope and promise of modern science. The NIH is funding a record number of research grants, with special emphasis on groundbreaking projects in areas that show the greatest potential for improving health, including genetic medicine, clinical research, and health disparities.

This research is vital, because we truly are on the cusp of finding the cures for some of our most debilitating and deadly diseases. And we continue to invest in the NIH to support research on improving minority health and narrowing the gap in areas such as cardiovascular health, diabetes, infant mortality, cancer, dental health, and fetal alcohol syndrome. We are also committed to reducing the incidence of HIV/AIDS among racial and ethnic minorities.

Together with other agencies in the Department of Health and Human Services, the NIH is playing an increasingly important role in protecting our homeland. The NIH has taken the lead on research on biodefense, and we are supporting the construction of specialized biosafety labs at universities and research institutions around the country to expand our capabilities in this critical arena. These and other investments made throughout the department will better prepare the nation for and protect us from a bioterror attack. They will also better prepare us for any public health emergency. We have already seen our investments pay off in our fight against the SARS outbreak and in the coordinated public health response to the West Nile virus—with the NIH playing crucial roles in advancing our understanding of the genetic blueprints of these viruses and devising and testing ways to combat them.

When I visit the NIH campus, I am always humbled and deeply impressed by the breadth and scope of NIH research. I salute all of the scientists who carry out NIH-supported research in Bethesda and across the country. Our work is making America healthier and helping to make the world healthier.

Tommy G. Thompson

Secretary of Health and Human Services

Mapping a Changing Landscape

Vast progress, exhilarating opportunities. The National Institutes of Health (NIH) has been a major force in guiding the U.S. medical research enterprise for more than a century, and the benefits are tangible—we have vaccines to protect us from devastating diseases, our blood supply is the safest in the world, and heart disease and stroke hold an ever-weakening grip on Americans' lives.

We continue to make major inroads against humanity's most enduring illnesses. The challenges we face, however, have been shifting. We are confronting new threats to our health and safety, from bioterrorism and West Nile virus to rising rates of obesity, diabetes, and Alzheimer's disease. With the help of the best scientific minds and dedicated public advisors, we have devised an ambitious but necessary plan to navigate this new landscape using sophisticated systems and tools and supporting the brightest and most innovative researchers.

As the 21st century begins to unfold and the genomic era becomes a reality, I am convinced that we can make quantum leaps in our knowledge about how to improve people's health.

When I came on board as NIH director in May 2002, I saw the need for a far-reaching plan to exploit the fast-breaking opportunities and face the challenges ahead to ultimately improve the health of all people. The doubling of the NIH budget has rightfully raised public expectations that we sustain our long record of cutting-edge contributions for the public good. My expectations are high as well.

So, we developed the *NIH Roadmap for Medical Research*—a short list of the most compelling initiatives that the NIH should pursue to make the biggest difference in medical research and health. The initiatives cut across NIH institutes and centers and bring together multiple disciplines. They also resonate with the needs and concerns of the public. You'll find details of the *NIH Roadmap* in this report.

As the 21st century begins to unfold and the genomic era becomes a reality, I am convinced that we can make quantum leaps in our knowledge about how to improve people's health. Powerful and unifying concepts of biology are emerging that hold the potential to lead to rapid progress. For example, in the past, cancer research was considered vastly different from heart or brain research. Today, with recent discoveries in molecular and cell biology, we know that biological systems obey common laws and follow similar pathways in both health and disease. As we begin to decipher the huge amounts of knowledge we have amassed, the scope, the scale, and the complexity of 21st century science demand that we devise newer ways to explore biology for the sake of improving health.

With me in this effort are thousands of researchers at academic and medical institutions around the country who receive NIH funding; a cadre of exceptional scientists here on the NIH campus in Bethesda, Maryland; and our partners from other federal agencies, nonprofit institutions, and industry.

This report is one of many efforts we at the NIH make to communicate our research results to the public and health professionals. In its pages, you'll find more about our world-class research, scientists, and programs. The landscape is changing, but we've set our eyes firmly on the horizon, and our view is of a place where all people are living healthier.

Elias A. Zerhouni, M.D.
Director
National Institutes of Health

At the Forefront of Medical Research

The National Institutes of Health (NIH), part of the U.S. Department of Health and Human Services, is the primary federal agency that conducts and funds medical research to improve people's health. It also trains scientists and communicates medical and health information to patients, their families, health care providers, and the public. As a leader in medical research, the NIH aims to make discoveries that will help prevent, detect, and treat disease and disability, from the common cold to the rarest genetic disorder.

This report will give you a glimpse of the full impact of NIH-supported discoveries on human health. Meet the scientists behind the breakthroughs, and learn how science works—how fundamental discoveries made in the laboratory are translated into medical advances that save lives. Find out about the valuable role citizens play in planning and implementing the nation's health research agenda, and hear from patients who are living longer and better than they ever expected because of NIH-supported research. Americans have witnessed great progress in medical research over the past 50 years, but great challenges remain. Learn how the NIH sets priorities and plans for the future. Some ambitious goals have been set for the next decade. Read about these goals on page 38, the *NIH Roadmap for Medical Research*.

With the support of the American people, the NIH annually invests over $28 billion in medical research. The overwhelming majority of the NIH budget, more than 80 percent, supports research conducted outside the NIH by a community of more than 212,000 scientists who work at universities, medical schools, hospitals, and other non-profit and for-profit research facilities throughout the United States and abroad. The NIH's in-house, or intramural, research program occupies the largest facility for medical research in the world, with 27 specialized research institutes and centers. About 10 percent of the NIH budget supports these laboratory and clinical research programs staffed by about 6,000 federal physicians and scientists mainly on the NIH campus in Bethesda, Maryland. This intramural program and the NIH Clinical Center provide the world with an unparalleled capacity for immediate research response to serious health challenges, such as AIDS, SARS, and West Nile virus.

The NIH relies on partnerships with universities and medical centers to do the research, and with community organizations to spread the word about new findings and health education programs. The NIH also works closely with the biotechnology and pharmaceutical industries to move promising new therapies through the research and development pipeline into the marketplace, where they can improve patient care.

The U.S. medical research enterprise is fueled by men and women who want to make a difference. They work in laboratories, at patients' bedsides, at computer workstations, and in

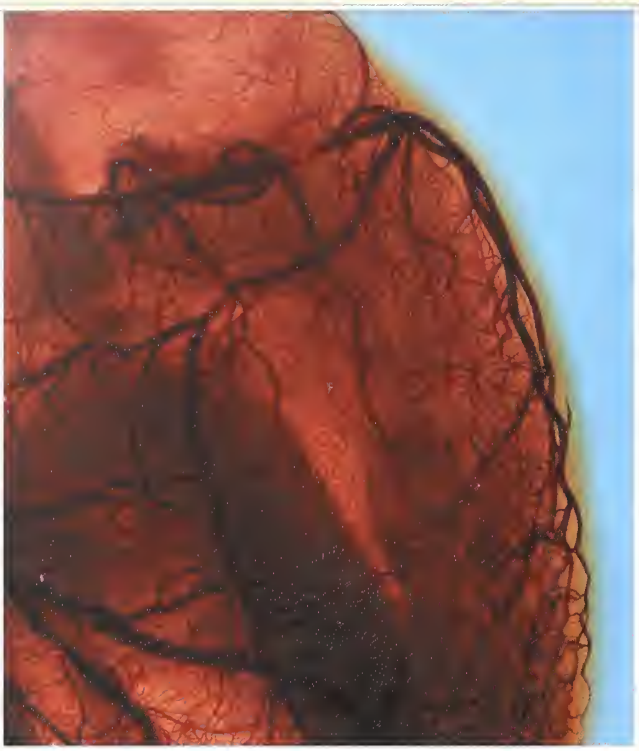
community centers, applying the principles of science and a drive to solve the problems of the day. They are facing the complexities of today's emerging threats by crossing disciplines—microbiologists are teaming up with engineers, computer specialists, and physicists. They are traversing geographic boundaries, working with people in separate laboratories, on distant campuses, or in far-away countries, because they share a common goal—to see people live healthier, better lives. The NIH is with them every step of the way.

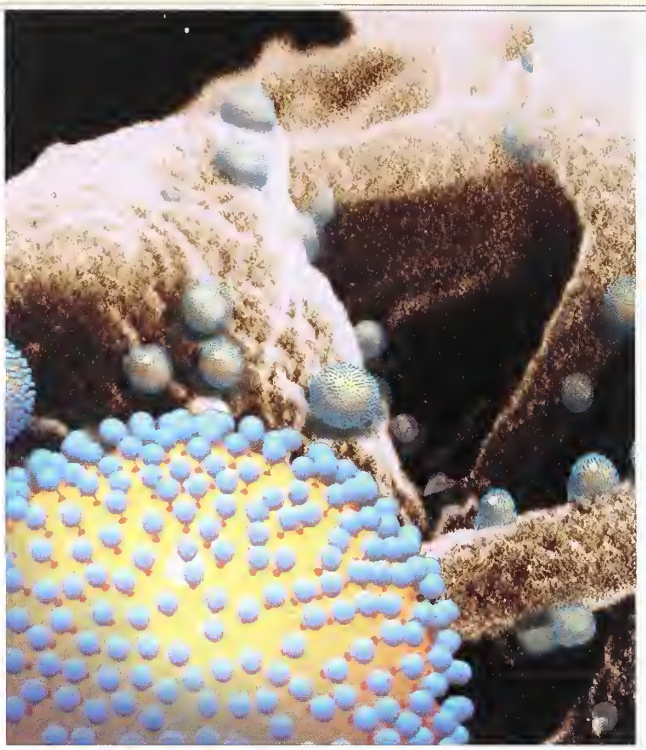
For more than a century, the National Institutes of Health has played an important role in improving the health of the nation. Its roots trace back to 1887 with the creation of the Laboratory of Hygiene at the Marine Hospital in Staten Island, New York.

Living Longer, Living Better

NIH-supported scientists have been working hard to improve human health for more than a century. Their efforts are paying off. Life expectancy in the United States has jumped from 47 years to 77 years, and more seniors are maintaining their independence and avoiding nursing homes. In fact, 2.4 million fewer Americans ages 65 and older are disabled than 1980 estimates anticipated for the early 21st century.

➤ Alfred L. Goldberg, Harvard Medical School, discovered how cells discard bad proteins—and surprised himself by designing a new cancer drug. See page 11.





A color-enhanced angiogram of the heart (left) shows a plaque-induced obstruction (top center) in a major artery, which can lead to heart attack. Right, computer-generated images of HIV (blue-dotted spheres) on scanning electron micrograph of a T cell.

Americans are enjoying tangible health benefits because of NIH-supported medical research:

Stronger Hearts, Clearer Vessels. Because of research funded by the NIH, heart disease and stroke take a vastly different toll than they would have if trends from the 1970s had continued. The NIH contributed in several ways: (1) identified behavioral factors that play a role, such as smoking, diet, and exercise; and (2) yielded drugs—through research in the lab and with patients—to control high blood pressure and reduce cholesterol, showed that aspirin can prevent heart disease and stroke, revealed that a clot-busting drug called t-PA can treat ischemic stroke patients, and produced other treatments such as angioplasty and coronary artery bypass surgery. As a result, death rates from heart disease and stroke fell by 40 percent and 51 percent, respectively, between 1975 and 2000.

A Vaccine to Prevent a Cause of Mental Retardation. A vaccine has virtually eliminated *Haemophilus influenzae* type b (Hib) in the United States, wiping out what used to be a leading cause of mental retardation in infants and children.

Lead Poisoning Is Way Down. After NIH-supported science demonstrated the harmful effects of lead on early cognitive development, national policies and laws were enacted in the late 1970s to remove lead from gasoline, paint for residential use, and household plumbing materials. As a result, children's blood lead levels dropped dramatically between 1976 and 1991. The NIH and the Centers for Disease Control and Prevention continue to study the effects of lead and work to reduce lead levels further, especially among African-American and Hispanic children, who are at increased risk of having elevated blood lead levels. A 2003 study supported by the National Institute of Environmental Health Sciences found that even low blood lead levels are linked to lower IQ and impaired memory.

Derailing a Deadly Epidemic. In 1995, at the height of the AIDS epidemic, the disease killed 51,670 people in the United States. Today, because NIH investments yielded vastly improved treatments and prevention strategies, the number of annual deaths among people with AIDS has dropped to 15,603—less than one third the 1995 level. There is much more to do, here and internationally, especially in resource-poor developing countries, which account for more than 95

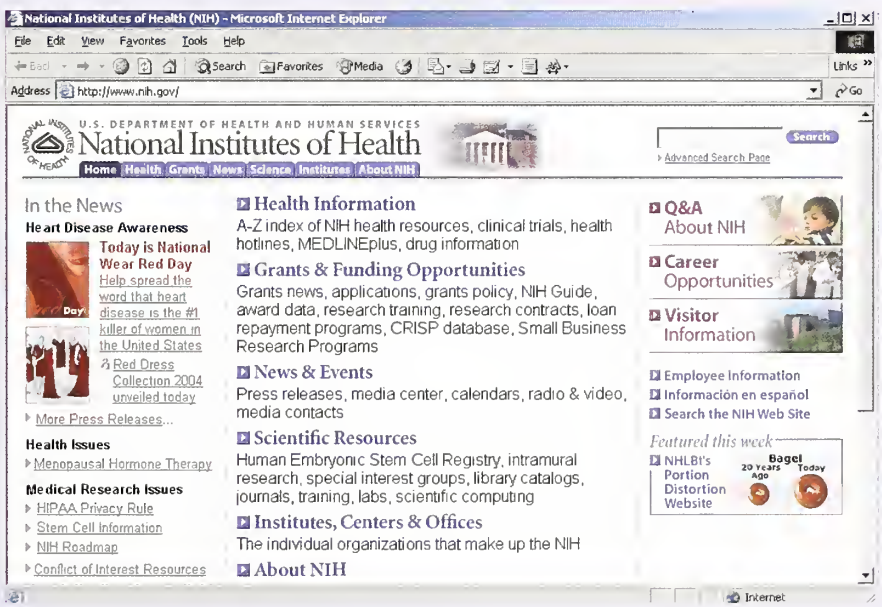
percent of all new infections. Although prevention programs, care, and treatment research remain essential, a vaccine is the best hope for stopping the spread of HIV/AIDS. Budget increases since 1998 have helped NIH efforts in identifying and testing dozens of candidate vaccines against HIV, the virus that causes AIDS.

Important Answers on Menopausal Hormone Therapy. Results of one of the largest disease prevention studies in the United States, the Women's Health Initiative, have given women and their doctors, for the first time, clear evidence that long-term menopausal hormone therapy carries significant risks. Women ages 50 to 79 taking estrogen plus progestin had an increased risk for heart attacks, breast cancer, strokes, and blood clots. These risks outweighed the benefits of fewer hip fractures and lower risk for colon cancer. In addition, the number of women over age 65 who developed dementia was greater in the menopausal hormone replacement group than in those taking the placebo. According to the Food and Drug Administration, estrogens and estrogens with progestins should be used at the lowest doses for the shortest duration to reach treatment goals, such as relief of hot flashes, night sweats, and vaginal dryness and to prevent bone loss.

AT YOUR FINGERTIPS

How can consumers get their hands on the best medical information? The NIH has the answer at *www.nih.gov*—the most popular government health and science Web site. Since October 1998, consumers have had easy Internet access to the medical literature and authoritative health information through a free service called MEDLINEPlus. This National Library of Medicine (NLM) resource has grown tremendously, containing detailed consumer information on 630 health topics, medical dictionaries and an encyclopedia, information on prescription drugs, interactive patient tutorials, health-related news items from daily newspapers, directories of health professionals and hospitals, and links to organizations and libraries that provide health information. As of October 2003, MEDLINEPlus was being consulted about 25 million times every month by three million visitors. The NIH is also home to *ClinicalTrials.gov,* a registry of about 8,800 trials of experimental treatments for serious or life-threatening diseases.

In its latest efforts to reach out, NLM launched a Spanish version of MEDLINEPlus in September 2002, followed by NIH Seniors' Health, launched in October 2003 and developed with the National Institute on Aging. Several other sites for the public have been launched as well: Tox Town (hazardous substances found in a typical town), Genetics Home Reference, and Household Products Database. Now NLM is working with public libraries and local organizations to bring MEDLINEPlus into communities around the nation.



Breaking Through the Silence. More than 70,000 people worldwide—about half of them children—have received cochlear implants. The device converts sound into electrical impulses to open a world of sound to deaf individuals. Children who get implants at an early age often learn to speak as well as children with normal hearing. Scientists supported by the National Institute on Deafness and Other Communication Disorders have shown that the brain can go 3.5 years without sound and still adapt quickly once sound is introduced through a cochlear implant. Young children with cochlear implants usually show age-appropriate brain responses within six to nine months. With 30 years of NIH investment in cochlear implant technology, the device has evolved from an experimental rarity to a commercially available tool that is helping thousands emerge from their silence.

- 10-year-old Will received his implant when he was a toddler. He was born profoundly deaf. At age 2, he became the youngest patient of John Niparko, M.D., an ear, nose, and throat specialist at Johns Hopkins School of Medicine in Baltimore who is a long-time NIH grantee and a surgeon who has mastered cochlear transplantation. It took three years for young Will to show demonstrable language development, but today he is excelling in his mainstream school. "There's nothing really that I can't do," says the baseball-playing fourth grader.

- Listening to 4-year-old Marie (below) sing one of the winter songs she learned in school—her voice clear and strong—is amazing, considering she was born deaf. She received a cochlear implant when she was 15 months old and now sings in the choir on Sundays. Says her mother June, whose hearing-impaired husband recently received his own cochlear implant, "It's something we never imagined possible for her."

Babies Sleeping Safer. NIH-supported research showed that sleeping on the stomach is a major risk factor for sudden infant death syndrome (SIDS). With a massive communications campaign called *Back to Sleep*, launched in 1994 by the National Institute of Child Health and Human Development, parents and caregivers got the message. Within two years, the number of infants placed to sleep on their stomachs dropped 66 percent. By the year 2000, SIDS deaths had been cut in half. The NIH and its partners have begun more intensive efforts to reach African-American communities, where SIDS rates remain high.

The cochlear implant creates a new way of hearing. There are about 250,000 Americans with severe to profound hearing loss who might benefit from a cochlear implant.

NIH PROFILE

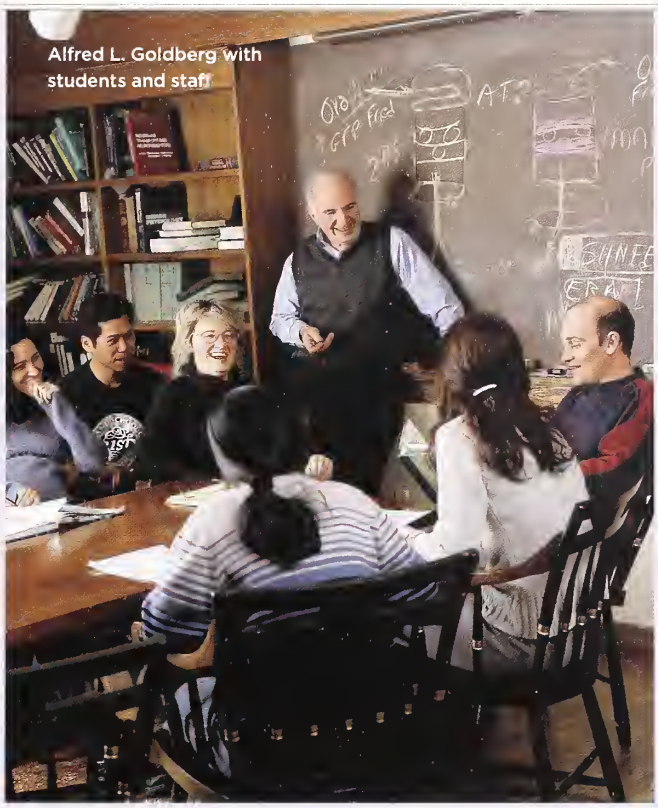
DRUGS THAT HIT THEIR TARGET

Novel drugs like Velcade kill cancer cells while sparing healthy cells.

When Gleevec (STI571, imatinib mesylate) was approved with great fanfare in 2001 for two hard-to-treat cancers, scientists promised the start of a new era in cancer treatment—a time when therapies are so specifically designed that they can precisely stop the disease with fewer harmful side effects. Gleevec was named one of the first of many potent, safer, targeted anticancer drugs whose designs resulted from new understanding of cancer at its molecular level.

Another promising drug won Food and Drug Administration approval in May 2003—on a fast track because of its potency against an often-fatal cancer of the bone marrow. The drug, called Velcade (PS-341, bortezomib), was approved to treat patients with multiple myeloma whose cancer is not responding to standard treatments. Multiple myeloma is the second most common blood cancer after non-Hodgkin's lymphoma. About 14,600 new cases are diagnosed in the United States each year.

The scientists who designed Velcade didn't plan on fighting cancer. Velcade was developed based on research done in the laboratory of Alfred L. Goldberg, Ph.D., a long-time NIH grant recipient and professor of cell biology at Harvard Medical School. In the 1970s, he set out to learn how cells destroy their own proteins and why and where. What he discovered was the 26S proteasome, a kind of garbage disposal in the cell that chews up abnormal or damaged proteins so they can't obstruct the normal workings of the cell. Proteasomes also control cell growth and many other processes in the cell by destroying regulatory proteins. Goldberg and three other Harvard professors, Thomas Maniatis, Ph.D.; Michael Rosenblatt, M.D.; and Kenneth Rock, M.D. (now at the University of Massachusetts Medical School), formed a company called Proscript, which developed drugs to inhibit the proteasome to slow down protein destruction and curb muscle wasting and inflammation. They showed that one of the inhibitors, later dubbed Velcade,



Alfred L. Goldberg with students and staff

could block growth of cancer cells and shrink tumors in mice. Eventually, their company was bought by Millennium Pharmaceuticals* of Cambridge, Massachusetts, which, with the National Cancer Institute (NCI), began testing Velcade in cancer patients and won speedy FDA approval.

"Normal cells can withstand reduced protein breakdown," explains Goldberg, 61. "Myeloma cells, however, go into suicide mode." He says he's even more excited about the potential of using Velcade to treat other cancers—lung, prostate, breast, and colon cancers. Millennium and NCI have more than 30 studies to test the drug in patients with these cancers. They are testing the drug alone and in combination with other cancer treatments to learn more about its utility and possible toxicity.

"NIH funding, through the National Institute of General Medical Sciences, allowed us to explore proteasome mechanisms and function and to study uses of proteasome inhibitors," Goldberg says. He also credits NCI for doing the early studies that confirmed Velcade's anticancer effects.

Goldberg says he's convinced that, as scientists continue to delve into how proteins are marked for destruction, even better drugs will be developed that block this marking process. "It is very likely that a number of drugs will emerge in the coming years that are even [better at targeting cancer cells] than Velcade."

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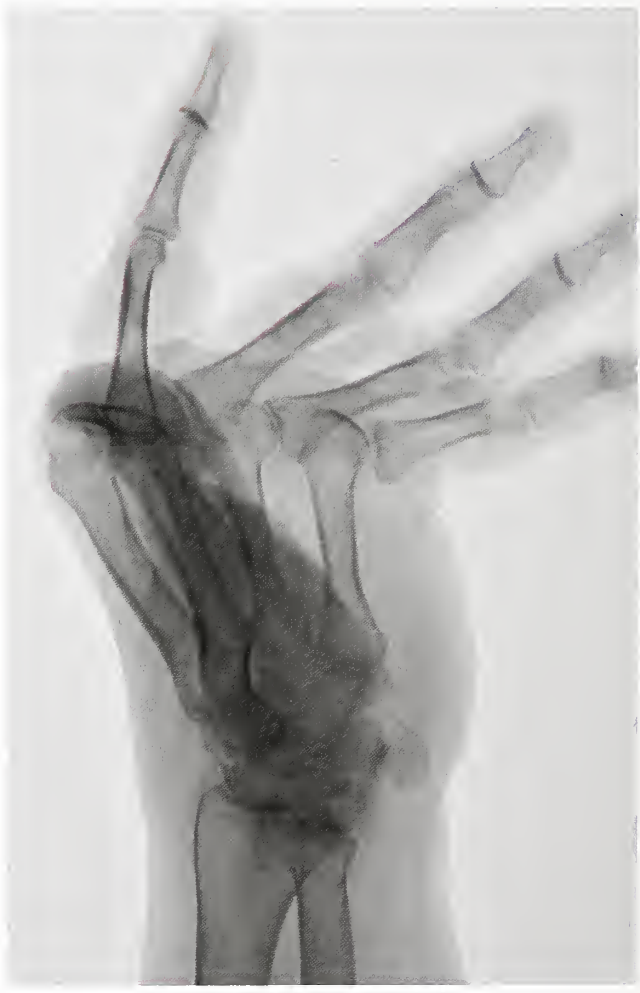
Keeping Diabetes Under Control. Research advances in the medical care of people with type 1 diabetes—such as better self-monitoring of blood glucose and better management of blood pressure—are making measurable, positive differences in patients' lives. Death rates between 10 and 20 years after diagnosis of type 1 diabetes, previously called juvenile-onset or insulin-dependent diabetes, had fallen from 8.4 percent in patients diagnosed in the late 1960s to 3.5 percent for those diagnosed in the late 1970s. A special coping skills training program developed by NIH-supported scientists enabled teenagers with type 1 diabetes to maintain better control of their diabetes. They experienced less depression and maintained confidence in their ability to manage their disease. More than 200 U.S. medical practices now use the training as part of their routine care of teens with diabetes.

A Revolution in Rheumatoid Arthritis Treatment. Not long ago, patients with rheumatoid arthritis faced a future of increasing pain and disability as their immune systems attacked and destroyed their joints. Because of the discovery of the role of tumor necrosis factor (TNF), a protein in the body that causes inflammation and plays a central role in joint destruction, scientists developed drugs to block TNF and found they could reduce the symptoms of rheumatoid arthritis and stop the joint damage. A wealth of new treatments, including Remicade (infliximab) and Enbrel (etanercept), are available that have the potential to prevent and heal the damaged joints of people with this painful disease—all because of the NIH's long-term investments in medical discovery.

Power over Depression. New medications developed in the past decade—Zoloft (sertraline hydrochloride), Serzone (nefazodone hydrochloride), and Lamictal (lamotrigine)—plus improved behavioral therapies have led to dramatically better treatments for depression. Patients have more treatment options and face fewer side effects. For millions of Americans, the debilitating symptoms of depression are now under control. New experimental medications such as memantine, riluzole, and felbamate are being tested by NIH researchers to improve treatments for unipolar depression, bipolar depression, and treatment-resistant bipolar disorder.



Tight glucose control, including frequent blood glucose monitoring (above), significantly reduces atherosclerosis and reduces damage to the eyes, nerves, and kidneys in people with type 1 diabetes. X-ray (below) shows destructive changes of the hand and wrist joints in a patient with rheumatoid arthritis.

Recent notable achievements from NIH-funded research

A Time of Discoveries

➤ Designer drugs created for blood clots.

Researchers have created designer drugs for preventing the blood clots that can cause strokes and heart disease during surgery. The resulting drugs have major advantages over the conventional drug, heparin. With support from the National Institute of General Medical Sciences, the scientists engineered the new drug by first cloning the gene for an enzyme—a kind of molecular scissors—called heparinase. They were then able to make a ready supply of heparinase, which they used to carve out the active sites of the heparins and design drugs that have been shown to be potent in rats. The next step is studies in humans.

➤ Straining water prevents cholera in Bangladesh.

Using common sari cloth to strain household water, residents in 65 rural villages in Bangladesh were able to cut their incidence of cholera almost in half. Cholera is a waterborne disease that causes severe diarrhea and vomiting, killing thousands of people around the world every year. This finding, by researchers supported by the National Institute of Nursing Research, should help stem the disease in poor countries where water treatment facilities are not available or where natural disasters, such as severe flooding, make boiling water impossible.

➤ Genomics helps predict response to chemotherapy.

Genomics helps predict response to chemotherapy. Patterns of genes that are active in tumor cells can predict whether patients with a cancer called diffuse large B-cell lymphoma are likely to be cured by chemotherapy, National Cancer Institute-sponsored scientists reported. The researchers used DNA microarray technology, which allows researchers to determine which genes are active within cells, to analyze thousands of genes in lymphoma biopsy samples and found that the activity of as few as 17 genes could be used to predict patients' response to treatment. Standard chemotherapy for the disease is effective in only 40 percent of patients. Profiling gene expression in patients' tumors may help clinicians decide which patients are suitable candidates for standard therapy and which should consider other options for treatment.

➤ Could exercise come in a pill?

Mice engineered to produce high amounts of a newly discovered enzyme in their muscles show the strength and endurance of those who do exercises—such as swimming or running—without doing the work. This finding could lead to an "exercise pill" that could provide the benefits of muscle activity to people with health conditions that prohibit exercising.

➤ Removing acupuncture's shroud of mystery.

Insertion of acupuncture needles causes measurable changes to connective tissue beneath the skin. Researchers supported by the National Center for Complementary and Alternative Medicine believe these changes are communicated along a signaling network, ultimately reaching the nervous system. These studies provide a tantalizing hypothesis for future research to understand the effects of acupuncture.

➤ Smallpox vaccine supply expanded.

Although smallpox was eradicated worldwide through a successful immunization program, there is still the potential for this virus to be used as an agent of bioterrorism. In 2001, the NIH supported a clinical trial to determine if the U.S. supply of smallpox vaccine could be used in diluted form to increase quickly the number of doses of the vaccine while still providing effective protection against the smallpox virus. The results of the study indicated that the vaccine could successfully be diluted at least five times and retain its potency, greatly expanding the number of people it could protect from the contagious disease.

FOR MORE DISCOVERIES, SEE PAGES 23 AND 47.

New Frontiers

Accomplishments that the most creative, the most hopeful among us could only dream about are being realized by scientists with NIH support. They are learning how to grow a functioning nerve cell from a stem cell, pinpointing the genes that malfunction in schizophrenia and Alzheimer's disease, and exploring the functions of the proteins that are the building blocks of every tissue and system in our bodies. This kind of groundbreaking basic research will take years to reach patients, but it promises to change medicine for the better.

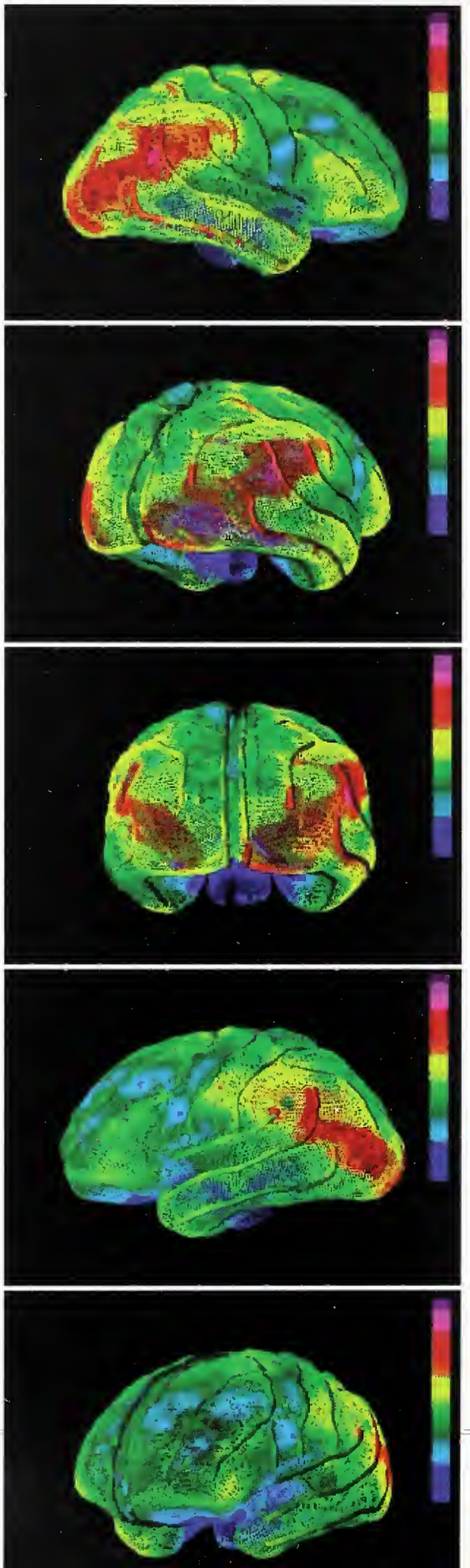
➤ Camillo Ricordi, University of Miami, invented the Ricordi Chamber as part of his effort to reverse diabetes. See page 20.

THE BRAIN

It controls all of our body's movements—every beat of the heart, each blink of the eye, a smile, a frown, a step up the curb. The brain dictates our thoughts, fears, imaginings. When it fails to work properly, it causes disorders that affect more than 50 million Americans annually. Not long ago, diseases of the brain and spinal cord left physicians feeling helpless and patients and their families feeling hopeless. Today, there is tremendous hope that many of these disorders can be treated and eventually conquered. In the past decade, researchers have made great strides in identifying genes that underlie Alzheimer's disease, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis, known commonly as Lou Gehrig's disease. Revolutionary imaging techniques can now reveal the dynamic changes that occur when the brain malfunctions.

■ The National Institute of Mental Health (NIMH) is expanding genetics research on schizophrenia in its Bethesda, Maryland, laboratories. At least half a dozen genes involved in schizophrenia have been found, and the intramural program is investigating how these genes interact and how they affect developing brain systems. Multidisciplinary teams will use mouse, fruit fly, and cell culture models; clinical studies; and brain imaging to explore how the vulnerability genes work at the molecular, cellular, and systems levels to discover the "risk architecture" of schizophrenia. Rather than rely on traditional clinical features of the illness, the NIH scientists will pursue changes in the brain underlying the altered thinking and emotions associated with this complex illness.

■ A newly released atlas of the brain will allow specialists to compare a patient's brain with those in a database of 7,000 digital images compiled by an international research consortium, led by the University of California at Los Angeles' Laboratory of Neuroimaging. The database includes scans from healthy people and from individuals with Alzheimer's disease, autism, schizophrenia, and fetal alcohol syndrome. Brain experts worldwide can access four-dimensional details of brain structure and function. The project was launched in 1993 with a grant from NIMH and has begun making the images available for use (see *www.loni.ucla.edu/ICBM*).



These maps from the Brain Atlas show variability in 3-D structure in normal male subjects. Hotter colors indicate increased variability.

■ As a complement to the Brain Atlas, the National Institute of Neurological Disorders and Stroke is funding the GENSAT (Gene Expression of Nervous System Atlas) to learn where genes are active in the mouse nervous system during development and adulthood. The goal is to superimpose information about gene expression in the mouse model on the four-dimensional images of the human atlas to learn more about brain function.

■ To mount a more focused attack on neurological disorders, the NIH is constructing a new building on the Bethesda campus—the John Edward Porter Neuroscience Research Center—in honor of the congressman from Illinois who was a champion of NIH-supported research. The Porter building will be one of the largest neuroscience research facilities in the world. It will bring together a critical mass of investigators from as many as 10 institutes or centers that conduct neuroscience research. The groups in the building will be organized by research themes such as neurodegeneration or mood and cognition rather than by institute. The Porter building's design features open spaces to foster inter-institute collaboration and cooperation among the investigators who will work there.

THE PROMISE OF STEM CELLS

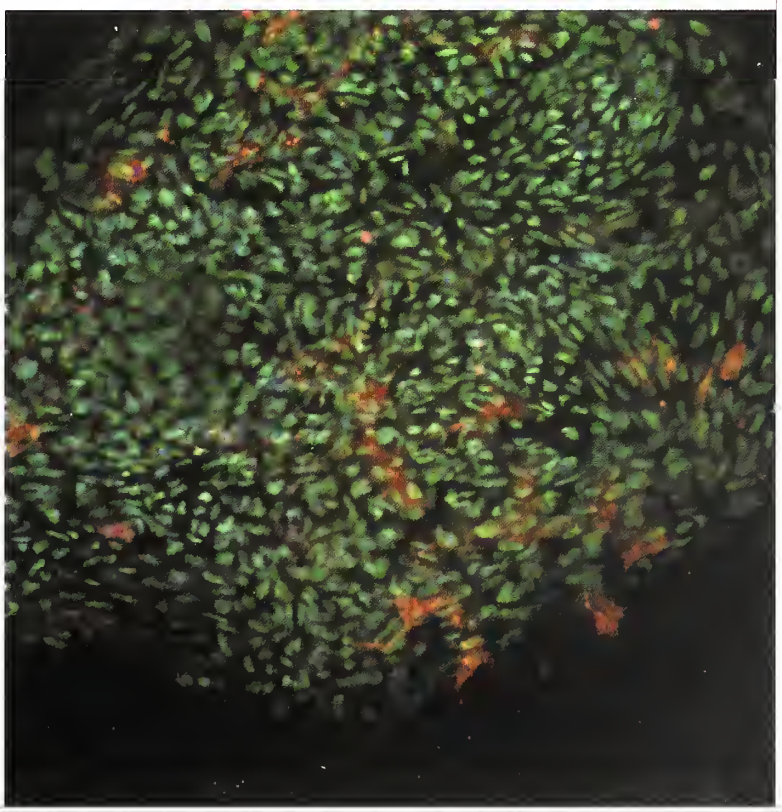
NIH is moving forward to develop the exciting potential of both adult and embryonic stem cells. Many of the individual Institutes and Centers of NIH support adult stem cell research designed to optimize the harvesting, experimental manipulation and delivery of these cells for repair or replacement of cells damaged through injury or degenerative processes. In the younger field of embryonic stem cell research, NIH-sponsored programs focus on the basic biology of the cells, making these cells available to investigators, training scientists to grow and differentiate these cells into specific cell types and supporting teams of scientists to work out the steps needed to translate this basic research into therapeutic applications.

Stem cells have two important characteristics that distinguish them from other types of cells. First, they are undifferentiated cells, meaning they have not yet matured into specialized cells like muscle cells or nerve cells, and they renew themselves for long periods through cell division. Second, under certain conditions, they can be induced to become cells with special functions such as the beating cells of the heart muscle or the insulin-producing cells of the pancreas. Scientists work primarily with two kinds of stem cells from animals and humans: embryonic stem cells and adult stem cells. Each has different functions and characteristics.

Connecting a gene with a disease was a slow, painstaking, and frequently imprecise process before the advent of the Human Genome Project. Consider two gene hunts, less than a decade apart. In 1989, scientists found the gene for cystic fibrosis after a nine-year search; in 1996, a gene for Parkinson's disease was mapped in only nine days and precisely described within nine months.

Stem cell researchers are finding new sources of stem cells and are methodically learning how to manipulate the cells to do their bidding.

■ NIH scientists at the National Institute of Neurological Disorders and Stroke were able to direct mouse embryonic stem cells to become specialized cells called neurons. Most important, when transplanted into rats that were missing dopamine-



When stem cells like these human embryonic stem cells divide, each new cell has the potential to remain a stem cell or become a cell with a more specialized function, such as a muscle cell or a red blood cell.

The Tooth Fairy's Secret

It all started when Songtao Shi's 6-year-old daughter, Julia, asked him to help her pull out a loose baby tooth. "Once it was out, we sat and looked carefully at the tooth," recalls Shi, a research dentist at the National Institute of Dental and Craniofacial Research. When he saw red tissue inside the tooth, he decided to bring it to his laboratory and take a closer look. The Tooth Fairy's loss was Shi's gain. By studying Julia's baby teeth as they fell out, along with exfoliated baby teeth from other children, Shi and his colleagues discovered a bounty of fast-growing stem cells. They named these cells SHED, for stem cells from human exfoliated deciduous teeth, because they exhibit important differences from "adult" dental pulp stem cells. They live longer, grow more rapidly, and with careful prompting in the laboratory, they can form several different types of cells. Shi and colleagues coaxed them into cells that form the major part of the tooth, called dentin, and into cells that induce generation of bone-forming cells, called osteoblasts. Their colleagues at the National Institute of Child Health and Human Development influenced SHED cells to act like neural and fat cells. The scientists speculate that SHED cells may one day be used to repair damaged teeth, induce the regrowth of bone, and treat nerve injury or disease. Now that the Tooth Fairy's secret is out from under the pillow, newly shed baby teeth may become an important source for stem cell therapy.

Songtao Shi and daughter Julia

producing neurons—the central feature of Parkinson's disease—the transplanted neurons formed functional connections and reduced symptoms of the disease.

- The same scientists transformed human embryonic stem cells into cells that produce dopamine, the neurochemical lost in patients with Parkinson's disease.

- Researchers at the University of Wisconsin, supported by the National Center for Research Resources, have succeeded in replacing a specific stretch of DNA in human embryonic stem cells. This technique opens the door to studying the function of specific genes within stem cells and provides a way to modify tissues derived from human embryonic stem cells in a very precise manner for use in treating patients.

- An NIH-supported scientist at the University of Minnesota isolated adult stem cells from human bone marrow. These cells show potential to mature into other cell types, including liver, neurons, and blood vessels.

- Scientists are working to identify genes that are involved in the differentiation of human embryonic stem cells, as well as those genes that permit embryonic stem cells to self-renew. This knowledge, along with research involving gene transfer techniques, may allow scientists to coax human embryonic stem cells into becoming insulin-producing beta cells to treat type 1 (insulin-dependent) diabetes.

THE PARTS LIST OF LIFE

DNA contains instructions for everything our cells do, from conception until death. The Human Genome Project (HGP), the international quest to decipher the genomes—the DNA in the cells—of humans and other organisms, will help answer a wide range of basic questions: How many genes do we have, how do cells work, how did living things evolve, how do single cells develop into complex creatures, and what exactly happens when we become ill? Answers to these and other questions promise to lead to an era of molecular medicine, with precise new ways to prevent, diagnose, and treat disease.

The Human Genome Project began in the United States in 1990, when the National Institutes of Health and the Department of Energy joined forces with international partners to decipher the massive amount of information contained in our genomes. The HGP has exceeded nearly all of its ambitious targets. HGP scientists have produced an increasingly detailed series of maps that help geneticists navigate through human DNA. They have also mapped and sequenced the genomes of important experimental organisms, such as the mouse and yeast.

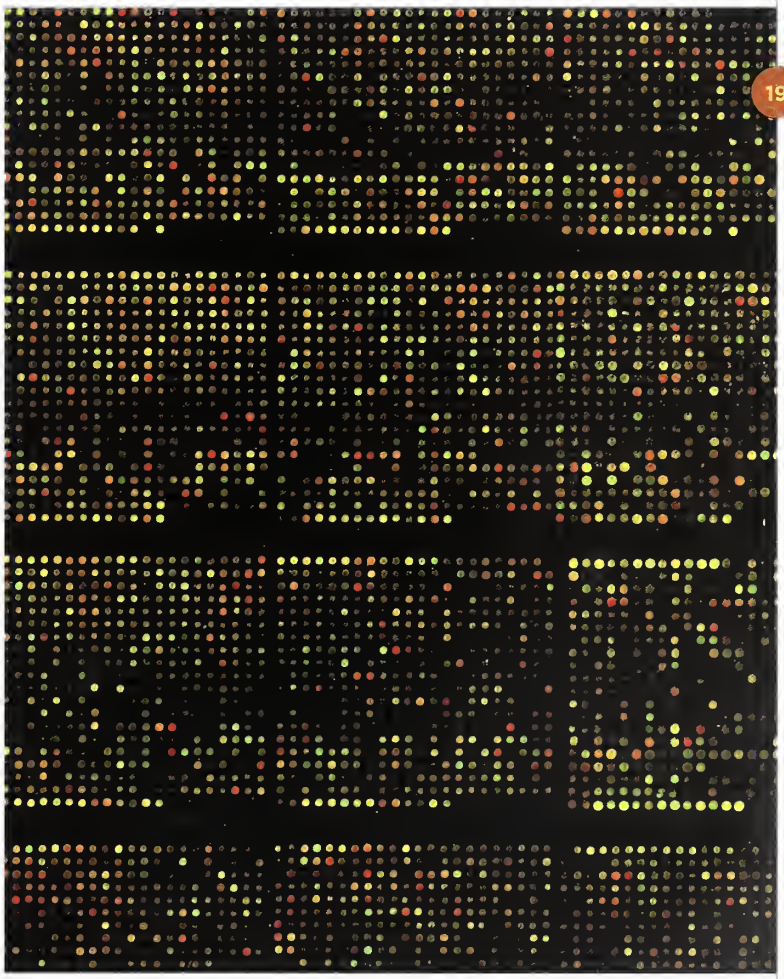
The HGP began transforming biology as soon as it started, because the information it generates has been disseminated rapidly through unrestricted, public databases. That information fuels today's heady pace of discoveries into the genetic basis of a wide range of disorders. These range from diseases caused by changes in single genes to more common conditions such as cancer, Alzheimer's disease, diabetes, and heart disease, where several genes interact with environmental factors to influence who develops a disease and when.

With this new knowledge, researchers are developing genetic tests to predict individual susceptibility to disease. As a result, diagnoses of many conditions will become much more thorough and specific. New drugs, derived from a detailed molecular understanding of common illnesses like diabetes and high blood pressure, will target molecules logically. Drugs like those for cancer will routinely be matched to a patient's likely response, making personalized medicine a reality.

Decades from now, many potential diseases may be prevented at the molecular level before they arise. These changes are not likely to come quickly. It will take a long time to understand the human genome. But this area of research will shape the practice of health care over the coming decades.

Scientists have been quick to mine the new trove of genomic data and use the genomic tools and techniques developed by the Human Genome Project. For example, when the project began in 1990, scientists had discovered fewer than 100 genes related to human disease. Today, more than 1,400 such genes have been identified.

The Environmental Genome Project, supported by the National Institute of Environmental Health Sciences, also reached a milestone in 2003, characterizing 200 genes that confer susceptibility to environmental agents involved in such chronic conditions as leukemia, heart disease, diabetes, and asthma. The aim of the project is to improve disease prevention and health management.



Geneticists are navigating through human DNA, electronically scanning long stretches of DNA to find genes in the sequence that may be responsible for a particular disease.

NIH PROFILE

A TRANSPLANT FOR DIABETES?

Researchers are testing implants to restore insulin production.

Ricordi (left) and the human islet isolation team

If the cells don't work, replace them. Easier said than done, of course. But Camillo Ricordi, M.D., and a core group of scientists from medical centers around the world have spent the past 20 years making step-by-step progress to do just that for patients with type 1 diabetes. They are transplanting islet cells from organ donors and remarkably improving blood glucose control, allowing most recipients to stop taking insulin, at least temporarily.

Islet cells produce the hormone insulin, which the body needs to control the amount of glucose in the blood. In type 1, formerly known as juvenile-onset diabetes, the islet cells are attacked by the body's own immune system and destroyed. Patients must compensate with insulin injections every day, and they face damage to their hearts, kidneys, and eyes, as well as risk of amputations.

For the transplant, which is still an experimental procedure available only as part of clinical studies, islet cells are isolated from donor pancreases and injected into the liver of patients with type 1 diabetes. Once in the liver, the cells develop a blood supply and begin producing insulin.

The procedure has worked in scores of patients with severe, long-term diabetes. "At three institutions, there have been a total of 80 to 100 patients getting transplants with a 90 percent success rate—meaning patients became insulin independent for more than 90 days," says Ricordi, chief of the Division of Cellular Transplantation at the University of Miami. "In the last two years, we haven't had a single transplant that didn't function." Patients are either completely off insulin or take substantially reduced levels of the hormone.

With all the excitement around these results—Ricordi won the 2002 Outstanding Scientific Achievement award from the American Diabetes Association—the road has been long, and there is more work to do. The question now is whether researchers can overcome existing limitations so that doctors can successfully treat large numbers of patients.

Ricordi, who was born in New York City and raised in Milan, Italy, says he's been supported by the NIH since he arrived in the United States in 1986 to do his postdoctoral work. He joined the lab of Paul E. Lacy, M.D., Ph.D., at Washington University in St. Louis as an NIH trainee in immunobiology of islet cell transplantation. Since then, he and colleagues around the world have systematically faced every challenge presented by this novel approach. He developed the automated method for isolating human islet cells and invented the Ricordi Chamber, the core element of the process, which is used by most researchers to separate the insulin-producing islet cells from other cells in the pancreas. No small feat, given that a mere 1 percent of each pancreas contains islet cells. Next he devised a way to keep the cells viable long enough to transport them long distances.

Ricordi, 47, is quick to share credit for the progress made in islet

cell transplantation with collaborators at the University of Minnesota; San Raffaele Institute in Milan; University of Alberta in Edmonton, Canada; Justus Liebig University in Germany; and his St. Louis colleagues, among others. He also spends a good deal of time with colleagues from Edmonton and Minneapolis, training researchers from around the world in islet separation, purification, and transplantation techniques, so that the science can move more rapidly. "It helps us, too. We're constantly trying to improve," he says.

Ricordi receives funding from three NIH components: the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Center for Research Resources (NCRR), and National Institute of Allergy and Infectious Diseases.

The University of Miami is also 1 of 10 Islet Resource Centers funded by NCRR, in cooperation with NIDDK and the Juvenile Diabetes Research Foundation International, to accelerate the research. Each center isolates high-quality human islet cells for transplant studies. "It would be tremendously expensive for every hospital to set up a facility to process islet cells for a few transplants a year. We process the cells and ship them to Baylor College of Medicine, for example, in Houston," says Ricordi.

Three big challenges remain. Because rejection is the biggest problem with any transplant, patients must take drugs to suppress their immune systems for the long term. These drugs can cause severe side effects. The scientists are experimenting with stem cells from the bone marrow of the donor to retrain the patient's system not to reject the transplant, but this work is in very early stages. Then they've got to find an unlimited source of insulin-producing cells. Not enough islet cells are available for all the patients who could benefit, so they are trying to engineer islet cells from human stem cells and are exploring other avenues as well.

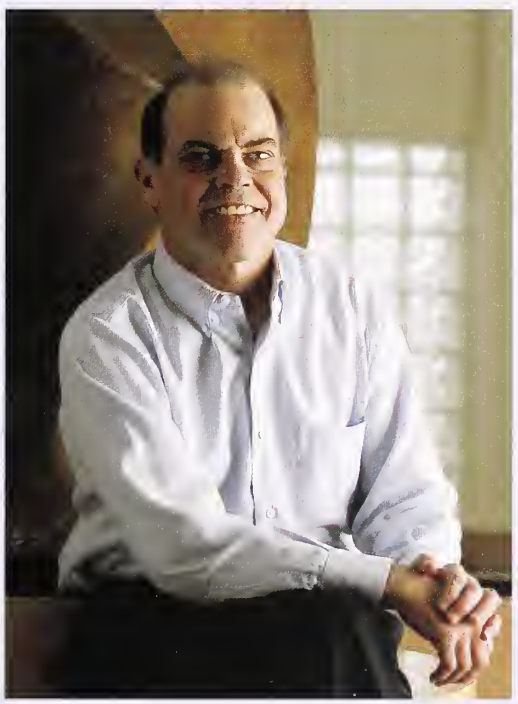
For the 1.5 million Americans with type 1 diabetes, especially the 150,000 with severe diabetes, Ricordi says that overcoming those large hurdles is a priority and a clarifying vision. At a recent lecture, he promised, "We will get this job done, and this is not a prediction. It is a promise!"

A HUGE RELIEF

Gary Kleiman remembers being diagnosed with diabetes just before his seventh birthday in 1960. "It was Easter time, and there was candy in the hospital. I offered some to my mother and the nurse. They flipped. 'You can't have that!'" Thus began a lifetime of worry—and deterioration.

By age 18, retinopathy, a common complication of diabetes, left Kleiman blind in his right eye. He had to leave college, where he was an art major and tennis player. The damage continued. His first kidney transplant followed in 1982, with a kidney donated by his mother. In 2001, he received a second kidney from his brother. By then, nerve damage was making it harder for him to sense when his blood sugar was getting dangerously low. He felt anxious all the time—until his islet cell transplant on November 1, 2002. He's been off insulin ever since. "This nine-month vacation has been remarkable," says the 50-year-old Kleiman. "The freedom from the stress of worrying about hypoglycemia [low blood sugar] is the biggest gift."

Kleiman is executive director for medical development at the University of Miami's Diabetes Research Institute, where Camillo Ricordi is director. He says he feels fortunate to have lived long enough to experience the triumph of a medical breakthrough. "We've come a long way, but still have a long way to go. I've watched Camillo Ricordi bridge so many of the forces out there, to be a voice for translational research, a voice for collaboration. Watching the progress has been almost as exciting as the transplant itself."



Use of genome technology has already yielded findings that point toward improved treatments for patients with, for example, cancer.

■ *Moving toward safer gene therapy.* Researchers at the National Human Genome Research Institute may have taken a major step toward safer gene therapy for patients. Most gene therapy experiments attempt to cure genetic illnesses by using a specially engineered retrovirus to insert normal, working copies of a gene into target cells in the body. But the technique has faced serious technical hurdles. The researchers designed a fast and easy way to find out where viruses land in the human genome and were able to show that the mouse virus used in gene therapy trials tends to insert itself at the beginning of genes in the target cell, potentially disrupting the way the gene works and causing problems for the patient. With this new knowledge, researchers plan to alter the mouse viruses so they control where the viruses insert into the genome.

■ *Oral drug unlocks silenced genes and cuts tumor size in mice.* The drug, called zebularine, shrank tumors by turning on tumor suppressor genes that had been shut down by a process called methylation. In DNA methylation, a methyl group is added to a stretch of DNA, locking or silencing that gene. When methylation silences a gene that controls cell growth or causes cell suicide, the cell will grow uncontrollably, and cancer develops. The fact that zebularine is effective when taken orally is good news, because ease of administration is difficult to achieve with cancer drugs. The work was a collaboration among the University of Southern California/Norris Comprehensive Cancer Center, University of Oregon in Eugene, University of Miami School of Medicine, and the National Cancer Institute (NCI). The research was supported by the National Institute of General Medical Sciences and NCI.

PROTEOMICS

Now that the complete sequence of the human genome is available, researchers are setting their sights on an even more difficult and complex goal—understanding the proteome, the complete set of proteins that make up a living organism. Some proteins build our cells, and other proteins work like miniature machines to allow us to think, smell, eat, and breathe. Proteins are indispensable molecules in our bodies, and each has a unique three-dimensional shape that is well suited for its particular job. The genes do the programming, but all of the information flows through the proteins.

The field of proteomics seeks to reveal the levels, activities, regulation, and interactions of every protein in the cell and how these quantities respond to a particular stimulus, such as a drug, a food, an infection, or a disease state or DNA alteration. Discoveries about the cells' protein machinery will likely yield important clinical applications. For example, proteomics knowledge could provide an understanding of the molecular basis of the cause and progression of heart, lung, and blood disorders, identify targets for new therapeutic interventions against diabetes and its complications, and lead to new methods for early detection and diagnosis of cancer. The field of structural biology aims to determine all the possible three-dimensional structures proteins can take. This information is critical, because a protein's structure usually dictates its function in the body, and misshapen proteins are the culprits behind many diseases, including cystic fibrosis, Alzheimer's disease, and countless others.

Science Chooses Mental Illness Genetics as a Top Breakthrough for 2003

Research on the genetics of mental illness, most of it funded by the National Institute of Mental Health, was named the number two scientific "breakthrough of the year" by *Science* magazine in its December 19, 2003, issue. The journal cited progress not only in identifying genes that increase one's risk of developing schizophrenia, depression, and bipolar disorder, but also in "unraveling" how the genes work in the brain to influence vulnerability.

The journal specifically mentions the finding by NIMH grantees at the University of Wisconsin that a variant of the serotonin transporter gene doubles the risk of depression following life stresses in early adulthood (see page 73). It points to NIMH researchers who found that the same gene variant biases the response of the part of the brain called the amygdala toward increased anxiety when frightening faces are viewed.

Also cited are discoveries by other NIMH researchers that a particular version of the *COMT* gene slightly increases risk of schizophrenia by impairing function of the prefrontal section of the brain. Work by this team is also credited for showing how the *BDNF* gene, which has been linked to bipolar disorder, affects memory in humans through effects on the part of the brain called the hippocampus.

Recent notable achievements from NIH-funded research

A Time of Discoveries

➤ Structure of last toxic anthrax protein solved.

Researchers supported by the NIH solved the three-dimensional structure of edema factor, one of the three toxic proteins responsible for the deadly effect of the anthrax bacterium, *Bacillus anthracis*. Edema factor was the last of the three to have its three-dimensional structure solved, an important step in designing antidotes.

➤ Diuretics are best choice for hypertension.

In a multicenter trial supported by the National Heart, Lung, and Blood Institute, diuretics were found superior to more costly calcium channel blockers, ACE inhibitors, and an alpha-adrenergic blocker in treating patients with high blood pressure and preventing heart failure or stroke.

➤ New drug available for opioid addiction.

Buprenorphine is a new medication developed through more than a decade of research supported by the National Institute on Drug Abuse. Unlike other medications that treat addiction, buprenorphine can be prescribed by any physician who receives certification and training by the Substance Abuse and Mental Health Services Administration.

➤ Aspirin prevents colon cancer recurrence.

Daily use of aspirin significantly reduced the incidence of colorectal polyps in patients with previous colorectal cancer, according to a study supported by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Cancer Institute.

➤ Anemia elevates risk of physical decline in the elderly.

Anemia doubles the risk that an older person will develop serious physical declines that can erode the ability to live independently, according to an epidemiological study supported by the National Institute on Aging. Anemia occurs when the body doesn't have enough red blood cells to carry oxygen from the lungs to other tissues. It affects about 13 percent of older Americans.

➤ Vaccine prevents stroke in mice.

An experimental vaccine interferes with inflammation inside blood vessels and greatly reduces the frequency and severity of strokes in mice that are genetically prone to stroke, according to a study by scientists at the National Institute of Neurological Disorders and Stroke. If the vaccine works in humans, it could prevent many of the strokes that occur each year. The researchers are planning a phase I clinical trial to test the safety of the vaccine in people at high risk for stroke.

➤ Tooth decay bacterium has its genome sequenced.

Scientists supported by the National Institute of Dental and Craniofacial Research have deciphered the genome of *Streptococcus mutans*. Now researchers can more systematically search for genes involved in the bacteria's ability to function. Building on this genome research may one day lead to new approaches for preventing and treating tooth decay.

➤ College drinking influenced by gene variant.

Researchers have identified a genetic factor that may predispose young people to harmful drinking habits. A team of scientists from the National Institute on Alcohol Abuse and Alcoholism and colleagues from George Washington University in Washington, D.C., interviewed college students about their alcohol consumption and then analyzed their genetic profiles, or genotypes. They found that students who shared a particular variant of the serotonin transporter gene (*5HTT*) consumed more alcohol per occasion, more often drank expressly to become inebriated, and were more likely to engage in binge drinking than students without the variant.

FOR MORE DISCOVERIES, SEE PAGES 13 AND 47.

Getting the Word Out

New research results can make their mark only if they are communicated to both the public and health professionals. The NIH works in partnership with many different organizations to communicate scientific results to the medical research community, health care providers, patients, the media, and the public. Partners include other federal agencies, state agencies, private-sector organizations, and national health care organizations.

➤ Genes, environment, and social factors play important roles in smoking addiction and cessation, according to Caryn Lerman, University of Pennsylvania. See page 28.

REAL MEN, REAL DEPRESSION

Depression affects about six million men every year. Yet many don't seek help. In April 2003, the National Institute of Mental Health (NIMH) launched the first national campaign to help men recognize the signs of depression and seek treatment. The campaign uses real people—a police officer, an architect, a student, a writer, and others—who tell their personal stories about depression, treatment, and recovery in a series of public service announcements. The message is simple: "It takes courage to ask for help. These men did. So can you." The public service announcements and news stories have reached an audience of nearly 200 million, and information has been translated into the languages used in South Africa. The NIMH *Real Men, Real Depression* Web site (*www.nimh.nih.gov*) has received more than two million hits.

THE HEART TRUTH—WOMEN AND HEART DISEASE

One in three American women dies from heart disease, yet only 9 percent of women identify heart disease as a top health concern. The National Heart, Lung, and Blood Institute launched *The Heart Truth* campaign in September 2002 with the American Heart Association, the Department of Health and Human Services' Office on Women's Health, WomenHeart: the National Coalition for Women with Heart Disease, and other groups to increase awareness that heart disease is the number one killer of women and encourage women to find out their personal heart disease risk and take steps to lower it. The centerpiece of the campaign is the Red Dress. First Lady Laura Bush launched the Red Dress Project with national media appearances, and the fashion industry contributed 19 designer dresses and a Red Dress pin. Sustained media coverage accompanied a 40 percent increase in calls to the campaign's toll-free phone line over one month. To measure increased awareness, the campaign will conduct a benchmark survey every three years (see *www.heart-truth.gov*).

Designer Carmen Marc Valvo conducts a final fitting of his red dress creation with Vanessa Williams at his studio. Williams joined other celebrities, models, and designers to raise women's heart disease awareness for *The Heart Truth's* Red Dress Collection 2004 during February's Olympus Fashion Week.

KNOW STROKE. KNOW THE SIGNS. ACT IN TIME.

The announcement in late 1995 that the most common type of stroke, acute ischemic stroke, can be successfully treated with a drug called t-PA created the need for a national plan to make this treatment rapidly available. The message was that timing is crucial. The optimum time to use t-PA to treat stroke patients is within three hours, but to be evaluated and receive treatment, patients need to get to the hospital within 60 minutes. The National Institute of Neurological Disorders and Stroke conducted a campaign, *Know Stroke. Know the Signs. Act in Time*, aimed at increasing public awareness of the symptoms of stroke and improving the health care delivery system. Consumer outreach is now geared toward higher-risk populations, such as African Americans and Hispanics. Each year, 700,000 Americans suffer strokes, costing the country an estimated $45 billion. More than three million Americans are living with some disability resulting from stroke (see *www.ninds.nih.gov/ health_and_medical/pubs/knowstroke.htm*).

DO YOU HEAR WHAT I HEAR?

WISE EARS! is a coalition of 94 public and private organizations and government agencies working to prevent noise-induced

hearing loss. The campaign is led by the National Institute on Deafness and Other Communication Disorders. Ten million Americans have already suffered irreversible hearing loss, and some 30 million individuals are exposed to dangerous levels of noise each day. Messages targeted to specific at-risk populations in all 50 states and territories—rural residents ("Bang! Boom! Buzzzzzz!") and AARP members ("WISE EARS! Last a Lifetime"), for example—have generated thousands of articles with readership in the millions.

BACK TO SLEEP

When research made clear that putting infants to sleep on their stomachs raised their risk of dying from Sudden Infant Death Syndrome (SIDS), the National Institute of Child Health and Human Development (NICHD) formed a coalition to launch a public awareness campaign in 1994 called *Back to Sleep*. Along with NICHD, the coalition consists of the Health Resources and Services Administration, American Academy of Pediatrics, Association of SIDS and Infant Mortality Programs (formerly the Association of SIDS Program Professionals), and SIDS Alliance. Private companies got involved—Gerber placed the *Back to Sleep* message on its cereal boxes, and Pampers printed it on the front of diapers. NICHD distributes free *Back to Sleep* publications and other materials in English and Spanish on reducing the risk of SIDS. Before the campaign, approximately 5,000 to 6,000 infants died unexpected and unexplained SIDS deaths in the United States each year. Those numbers have dropped by half.

African-American infants are at a greater risk for SIDS. Since the start of the campaign in 1994, the SIDS rates for both whites and African Americans have declined by about 50 percent, but the SIDS rate for African-American babies is still double that for whites. To address this issue, the *Back to Sleep* campaign sponsors, the National Black Child Development Institute, and several other organizations worked together to develop materials for an initiative to reduce SIDS in African-American communities. Copies of materials may be ordered online at *www.nichd.nih.gov/sids*.

The *Back to Sleep* campaign has been teaching parents and caregivers that placing infants to sleep on their backs reduces their risk of dying from Sudden Infant Death Syndrome. Death rates from SIDS have been cut in half.

SMALL STEPS, BIG REWARDS

When the Diabetes Prevention Program clinical trial showed that modest weight loss and regular physical activity could cut the risk of developing type 2 diabetes by more than half, the NIH took action. The *Small Steps, Big Rewards* campaign was launched in November 2002 to spread the word that there is hope for the millions of Americans who are at risk for developing diabetes. Small changes can translate into big rewards. The NIH and the Centers for Disease Control and Prevention lead the effort, which involves more than 200 public- and private-sector partners. It includes an awareness campaign, lifestyle-change tools for consumers, a health care provider's tool kit, and Web-based resources, plus outreach through businesses and consumer groups. For more information, visit *www.ndep.nih.gov/campaigns/campaigns_index.htm*.

YOUR QUESTIONS ANSWERED

NIH clearinghouses or information services help the public get the most accurate, up-to-date information on any disease. At last count, 29 toll-free information lines provide specifics on everything from kidney and urological diseases to AIDS clinical trials to mental illness. Visit *www.nih.gov/health/infoline.htm* for a full listing.

One of the most popular resources is the Cancer Information Service (CIS), which provides free cancer information and education to cancer patients, their friends and families, the public, and health professionals. Through a network of 14 regional offices, the CIS serves the United States, Puerto Rico, the U.S. Virgin Islands, and the U.S. Pacific Territories. Services include personalized information and recorded messages in English and Spanish through a toll-free number (1-800-4-CANCER); a smoking cessation service called Quitline (1-877-44U-QUIT); free National Cancer Institute publications and fact sheets in hard copy and via the Internet (*http://cancer.gov*); a Web-based instant messaging service called LiveHelp; and a TTY line for the hearing impaired. Finally, the CIS works with regional organizations to bring

NIH PROFILE

CUTTING THROUGH THE SMOKE

Researchers are crossing disciplines to untangle the biological and environmental threads of nicotine addiction.

Kicking the smoking habit is about much more than willpower. "The more I learn, the more I realize that it's extremely complicated," says Caryn Lerman, Ph.D., director of the NIH-supported University of Pennsylvania Transdisciplinary Tobacco Use Research Center (TTURC). "I realize how hard it will be, and how long it will take, to really get to the point where we have a very comprehensive understanding of addiction—and a sufficient foundation of knowledge to design better prevention and treatment strategies based on that."

The University of Pennsylvania TTURC is one of seven academic research centers around the country devoted to studying various aspects of tobacco use and nicotine addiction. As its name suggests, it crosses disciplines with abandon, delving into psychology, genetics, pharmacology, neuroscience, medicine, epidemiology, communications, and public policy.

The Penn TTURC has a full-time staff of about 40 and several million dollars in federal grants from the National Cancer Institute and the National Institute on Drug Abuse—not to mention funding from the Robert Wood Johnson Foundation to study the public policy and communication pieces of the tobacco puzzle.

That may seem like an awful lot of money, but tobacco is no ordinary research subject. Consider these facts, some of which may be depressingly familiar, from TTURC's Web site:

- 43.5 million U.S. adults—almost one in four—smoke cigarettes.
- Nearly one in every five deaths in the United States is a result of smoking, making it the leading preventable cause of death.
- Roughly 3,000 Americans die each year because of exposure to secondhand smoke, and more than 1,000 infants die because their mothers smoked during pregnancy.

Lerman, age 44, got hooked on cancer genetics while working in Fox Chase Cancer Center's behavioral-research group. "My initial work was on the psychological aspects of genetic testing—understanding how all this exciting research coming out of the Human Genome Project was actually going to impact people's lives, and whether people will want to know their genetic futures," she says. "How would they react to the information psychologically? Would they change their behavior?"

That, in turn, led to a deep interest "in the question of whether we could characterize the genetic underpinnings of different behaviors that relate to cancer," she says. "And, of course, one of the most important cancer risk behaviors is tobacco use."

About seven years ago, while at Georgetown University, she and colleagues at the National Cancer Institute began a series of studies to look for specific genetic effects on smoking behavior. One study

education messages to minority populations and those with poor access to health care.

The NIH Web site, *www.nih.gov*, is also full of information and resources for the public. It contains an extensive health information database where consumers can search for information on specific diseases, medical procedures, research studies, and much more. *Word on Health* contains reprintable news capsules based on NIH-supported research that can be picked up by local newspapers. The NIH also produces a weekly radio news service to distribute breaking news and health information. Teachers and students can find a wealth of resources about new medical technologies and scientific advances. The NIH aims to attract young people to medical careers and improve science literacy in adults and children.

examined the effects of giving smokers relevant information about their genetic susceptibility to lung cancer—to see "whether we could overcome a sense of invulnerability and motivate them to quit smoking," she explains. "We discovered that we did motivate them a great deal by giving them biological feedback. However, despite a really high level of motivation and many quit attempts, most people in the study were not able to quit smoking."

"That's when I became more interested in the problem of addiction," she adds. "Because it's not just a matter of wanting to quit. We have to also consider the biology."

"The candidate genes that we had focused on initially included the genes in the dopamine and serotonin pathways, as well as genes involved in the metabolism of nicotine," Lerman explains. By studying those genes and their relationship to the effectiveness of treatment, she and her colleagues thought they might be able to identify smokers who are most likely to respond to the antidepressant drug bupropion—and those who aren't.

"Instead of using a one-size-fits-all model of smoking treatment, we hope that, through genetics research, we can develop a more rational way of tailoring treatment to an individual's genetic profile."

In a 2002 paper studying changes in *CYP2B6,* a gene that codes for an enzyme involved in brain metabolism of nicotine, Lerman's team reported that smokers who have a change in the gene "experience greater increases in cravings for cigarettes and are about 1.5 times more likely to relapse during the treatment phase than smokers who do not have the variant." The study also showed that bupropion may lessen these effects, especially among women.

A study published in October 2003 showed that smokers with a specific combination of two genetic variants related to dopamine may be more likely to remain abstinent and less prone to relapse when trying to quit smoking. This research "underscores the importance of not limiting genetic investigations of smoking behavior to single gene effects," Lerman says.

More work needs to be done, but Lerman can see a future when a smoker will go to the doctor for a panel of genetic tests and a psychosocial assessment and walk away with the treatment plan most likely to work for him or her. Lerman says, "We could be much more effective if we could tailor therapy based on knowledge of the smoker's biological as well as social needs."

Excerpted with permission from an article by Samuel Hughes for the January/February 2003 Pennsylvania Gazette, *the University of Pennsylvania's alumni magazine.*

NEW TOOLS, NEW APPROACHES

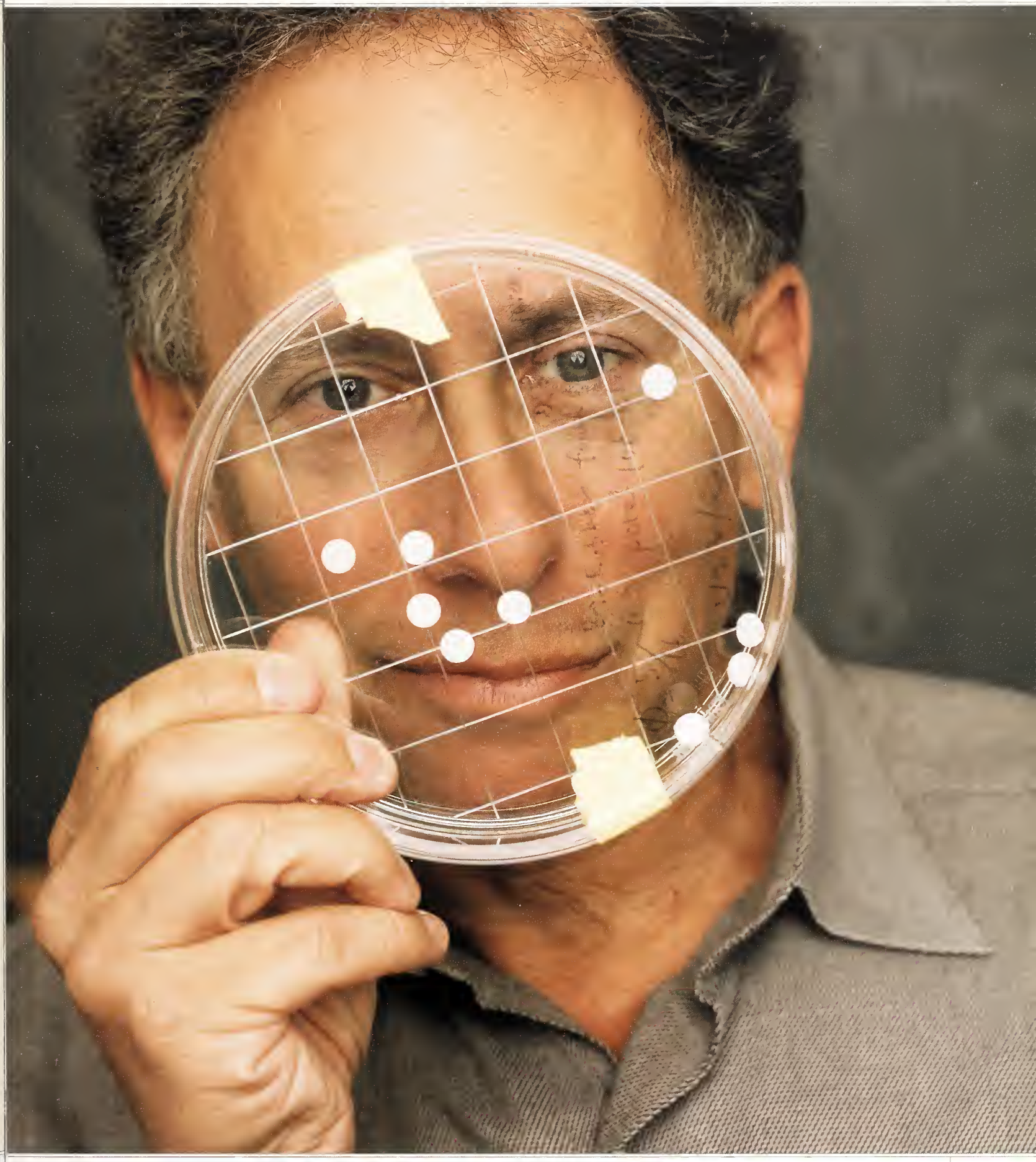
Through a $70 million, five-year initiative funded by the National Cancer Institute and National Institute on Drug Abuse, with an additional $14 million from the Robert Wood Johnson Foundation, seven universities have formed a network called Transdisciplinary Tobacco Use Research Centers to study new ways to combat tobacco use and its consequences.

- **Brown University** Identifying familial, early childhood, and lifetime psychiatric factors that determine initiation of smoking and response to treatment.
- **University of California at Irvine** Revealing links between specific personality traits and early initiation of cigarette smoking.
- **University of Minnesota** Examining approaches to reduce tobacco exposure for people who are unwilling or unable to quit.
- **University of Pennsylvania** Studying the role of genetic and environmental factors in smoking initiation and addiction, especially among students with depression.
- **University of Southern California** Studying cultural influences on tobacco use across cultures, including youth of Chinese, Vietnamese, Korean, Filipino, Mexican, South and Central American, and Middle Eastern descent.
- **University of Wisconsin** Developing a computer-based support system as a tool for preventing relapse among people who are trying to quit.
- **Yale University** Investigating the links among depression, gender, and smoking.

Working with Industry and Academia

The NIH's mission is to uncover knowledge that will lead to better health for everyone. The road from laboratory research to development of new drugs and therapies is long and risky. The NIH, private industry, and academia all play crucial roles along the way.

➤ Robert S. Langer, Massachusetts Institute of Technology, engineers new tissue and innovative drug delivery systems. He works with industry so his inventions will help people. See page 34.



Michael S. Brown, M.D., and Joseph L. Goldstein, M.D., won the Nobel Prize in Medicine for determining how the body metabolizes cholesterol. Their research led to the cholesterol-lowering drugs called statins.

Public investment in medical research has stimulated the growth of a highly educated and highly trained workforce at universities, academic medical centers, and small and large companies across the country. Over the past 20 years, the number of Ph.D. faculty in U.S. medical schools has grown by 88 percent. The doubling of the NIH budget has catalyzed new construction and renovation by U.S. medical schools with a three-fold increase in capital investment from 1990 to 2007.

Federal investments in biomedical research have increased in tandem with new investments by the private sector. For example, research and development (R&D) spending by members of the Pharmaceutical Research and Manufacturers Association exceeded the NIH budget for the first time in 1991. As the NIH has accelerated its investment in basic and clinical research, the pharmaceutical industry has boosted its work to bring new cures to market.

"Without the funding the NIH produces, both in its extramural and intramural programs, some of the basic discoveries that are the foundation by which we discover drugs would not have been possible," says Cecil B. Pickett, Ph.D., president of the Schering-Plough Research Institute, in Kenilworth, New Jersey. He points to NIH support of the research done in the laboratories of Michael S. Brown, M.D., and Joseph L. Goldstein, M.D., at the University of Texas Southwestern Medical Center in Dallas. The two men, both of whom received their research training in NIH intramural laboratories, won a Nobel Prize in Medicine for clarifying how the body metabolizes cholesterol. Their research led the pharmaceutical industry to develop cholesterol-lowering statin drugs to prevent heart disease in millions of Americans.

"There needs to be some longevity to the funding of basic research," continued Pickett, who is a member of the NIH Advisory Council to the Director, a 20-member panel that advises the NIH on policy and planning. Industry can't provide that longevity, he says. "We have more acute demands placed on us to demonstrate the shareholder value through innovative new medicines. It's difficult for industry to invest in long-term, purely fundamental basic research." Good thing the NIH does, he says, pointing to research on the human genome, which he calls "really fundamental to some of the things we'll do over the next 10 years." Pickett says that industry is beginning to use some of that basic knowledge in many of its early drug discovery programs.

BENCH TO BEDSIDE

Each year, hundreds of new inventions are made in NIH laboratories. The Office of Technology Transfer moves these inventions through licensing to the private sector for development. The licenses provide rights to use NIH technologies in return for royalty fees and, in the case of commercialization licenses, a commitment to bring the technology to the market.

In the past 10 years, more than 1,800 licenses to inventions made by NIH intramural researchers have enabled commercial partners to develop more than 20 life-saving drugs, vaccines, and diagnostics and more than 100 other biomedical products. Examples include the HIV Test Kit, marketed by Abbott and others; Zenapax (daclizumab), manufactured by Hoffmann-La Roche to prevent acute kidney transplant rejection; and Fludara

(fludarabine), marketed by Berlex as a treatment for chronic lymphocytic leukemia.

LEVERAGING RESOURCES

The NIH makes special efforts to involve industry for its expertise and productivity to move early-stage, promising technologies forward. One mechanism, called a CRADA (Cooperative Research and Development Agreement), provides an opportunity for NIH investigators to join with their colleagues from industry in the pursuit of common research goals. The purpose of a CRADA is to make government facilities, intellectual property, and expertise available for collaborative interactions to speed development of scientific and technological knowledge into useful, marketable products. The arrangement allows government scientists to leverage their own research resources to facilitate the development and commercialization of health care pharmaceuticals and products. Companies also can leverage their own R&D efforts while collaborating in state-of-the-art NIH research. For example, the vaccine Havrix prevents hepatitis A infection in soldiers and travelers worldwide because of CRADAs that licensed NIH inventions to SmithKlineBeecham, which did safety and efficacy testing and bulk manufacturing.

PARTNERS IN PROGRESS

Sometimes the NIH calls on the private sector for help with a particularly complex problem. The resulting partnerships do more than either the government or industry could do alone. The Foundation for the National Institutes of Health was established in 1996 by the United States Congress to support the mission of the NIH—improving health through scientific discovery. The foundation identifies and develops opportunities for innovative public-private partnerships involving industry, academia, and the philanthropic community. Three such opportunities are:

- **Grand Challenges in Global Health** A partnership launched in January 2003 by the Bill and Melinda Gates Foundation with the NIH, the Grand Challenges in Global Health Initiative, seeks to overcome scientific obstacles to solving the major health challenges of the developing world. The Gates Foundation began the initiative with a $200 million grant. The first 14 Grand Challenges were released in October 2003 (see box). The challenges are heavily oriented toward controlling infectious diseases, which account for the most profound disparities in health outcomes between developed and developing nations. The Foundation for the NIH is overseeing the process for awarding research grants that address the challenges.

- **Better Than Pain Relief** The Osteoarthritis Initiative (OAI) partnership is poised to do something that neither government

Grand Challenges in Global Health

Improve childhood vaccines:

1. Create effective single-dose vaccines that can be used soon after birth.

2. Prepare vaccines that do not require refrigeration.

3. Develop needle-free delivery systems for vaccines.

Create new vaccines:

4. Devise reliable tests in model systems to evaluate live attenuated vaccines.

5. Solve how to design antigens for effective, protective immunity.

6. Learn which immunological responses provide protective immunity.

Control insects that transmit agents of disease:

7. Develop a genetic strategy to deplete or incapacitate a disease-transmitting insect population.

8. Develop a chemical strategy to deplete or incapacitate a disease-transmitting insect population.

Improve nutrition to promote health:

9. Create a full range of optimal, bioavailable nutrients in a single staple plant species.

Improve drug treatment of infectious diseases:

10. Discover drugs and delivery systems that minimize the likelihood of drug-resistant microorganisms.

Cure latent and chronic infections:

11. Create therapies that can cure latent infections.

12. Create immunological methods that can cure chronic infections.

Measure disease and health status accurately and economically in developing countries:

13. Develop technologies that permit quantitative assessment of population health status.

14. Develop technologies that allow assessment of individuals for multiple conditions or pathogens at point-of-care.

NIH PROFILE

GOING FOR THE IMPACT

Robert Langer is an engineer who wants to change the world. He's bringing industry along for the ride.

Biorubber, microspheres, timed-release polymers, transdermal patches. Robert S. Langer, Sc.D., is a long-time NIH grantee who has had a hand in developing all kinds of innovative ways to engineer new tissue and deliver drugs to their precise targets in the body. Burn victims and patients with certain cancers and heart disease are better for it.

"I'm an engineer. I try to solve problems," Langer says. His reasoned approach has yielded more than 500 patents; more than 40 products resulting from his work are now on the market or in human testing. "I want to see science do good, to help people," says Langer, a professor of chemical and biomedical engineering at the Massachusetts Institute of Technology in Boston.

"I'm an engineer. I try to solve problems. I want to see science do good, to help people."

The 55-year-old's success in that endeavor has earned him accolades from every corner. *Discover Magazine* named him one of the 20 most important people in medical technology. *Forbes* selected him as one of the 15 innovators worldwide who will reinvent our future. In 2002, Langer won the $500,000 Draper Award, engineering's version of the Nobel Prize.

Throughout his career, Langer has received major support from the NIH. Today, he has grants from five NIH institutes. "The NIH has been the single biggest supporter of our lab," he says. "It enables us to do research. The money gives you the freedom to come up with the ideas you come up with—and those ideas can hopefully change the world in a better way.

"The NIH's investment is amplified enormously by biotech companies," he adds. For example, the field that he helped launch, controlled drug delivery, includes things like transdermal patches used for nicotine replacement therapy, inhalation therapy being studied for diseases such as diabetes, and drug-infused microchips. It is a $20 billion U.S. industry. In terms of health benefits, Langer claims, more than 10 million people in the United States alone use these kinds of systems.

Early in his career, Langer realized that industry had to figure

prominently if he wanted his inventions to reach the public. The private sector has the capacity and expertise to do final-stage testing, large-scale manufacturing, and obtain Food and Drug Administration approvals that academia does not. At first, he was swimming against the tide. Now he's seen as a visionary. He told the *Boston Globe* in a May 2003 article, "Some academics feel science should be pure, so they avoid interactions with companies. But when done well, I think the benefits are enormous—in treatments for disease, in new companies, in jobs." Langer has launched at least a dozen biotech firms and advises several more. More than 100 companies hold licenses to his patents. That means his discoveries reach the marketplace to help people.

One example is the Gliadel Wafer. In the mid-1980s, Langer and Henry Brem, M.D., a neurosurgeon at the Johns Hopkins University who had worked with Langer in the lab of renowned cancer researcher Judah Folkman, M.D., created a dime-size wafer to deliver chemotherapy directly to a site in the brain where a tumor has been removed. The Gliadel Wafer became the first therapy in more than two decades to extend the lives of patients with a deadly brain cancer called glioblastoma.

Langer and colleagues in June 2002 reported development of a new flexible plastic called biorubber. Biorubber can be impregnated with medicine or serve as a scaffold that can stretch and snap back like a rubber band, similar to human tissues such as the lungs' air sacs. The researchers are sharing samples with scientists around the world to test biorubber's utility in various settings.

Langer's work has also made possible the drug-eluting stent, which became available to patients with heart disease in 2003. Used for patients with life-threatening narrowing of the arteries, one such stent is marketed by Johnson & Johnson and coated with a drug called rapamycin that is slowly released into the blood vessel to prevent restenosis—narrowing of the vessel that the stent was used to widen. He says he expects the new stents will save 100,000 lives. Sounds like Langer is making good on his goal of changing the world, thousands of patients at a time.

Malaria, which is endemic in parts of the developing world, is a focus of the Grand Challenges in Global Health Initiative.

nor private industry could accomplish alone—establish a database of radiological images, biomarkers, and physical exams as objective and measurable standards for the progression of this painful and disabling disease. New therapies are desperately needed by the millions of people, most of whom are 65 and older, with osteoarthritis. The seven-year project to recruit 5,000 men and women age 50 or older at high risk for developing osteoarthritis of the knee is funded by several NIH institutes, along with the pharmaceutical companies Merck, Novartis, and Pfizer. The data collected through the OAI will be available to researchers worldwide to quicken the pace of scientific studies and to speed progress toward better treatments.

■ **Boosting Clinical Trials Participation** The NIH has awarded grants to six cancer centers involved in a unique public-private partnership to devise creative ways to increase the number of people who participate in early-phase clinical trials. Friends of Cancer Research initiated this groundbreaking collaboration between the National Cancer Institute and the Foundation for the National Institutes of Health in partnership with five pharmaceutical companies: Aventis, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, and Novartis. With only 3 to 4 percent of newly diagnosed adult cancer patients entering clinical trials each year, this partnership may give hundreds more cancer patients a chance to participate in early-phase clinical trials. Its intent is to shorten the time it takes for promising therapies to move from the laboratory bench to the patient's bedside.

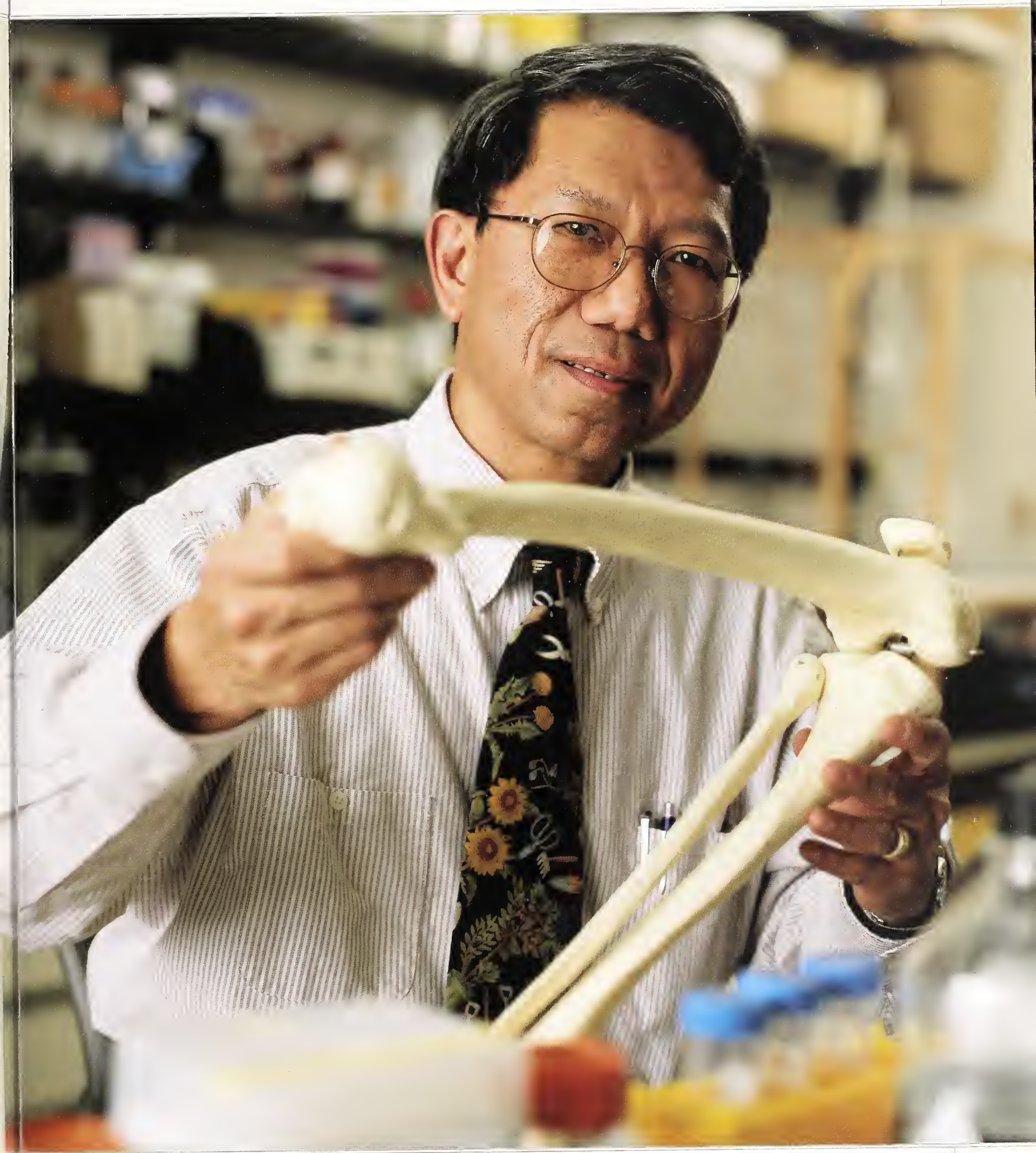
Charting the Future

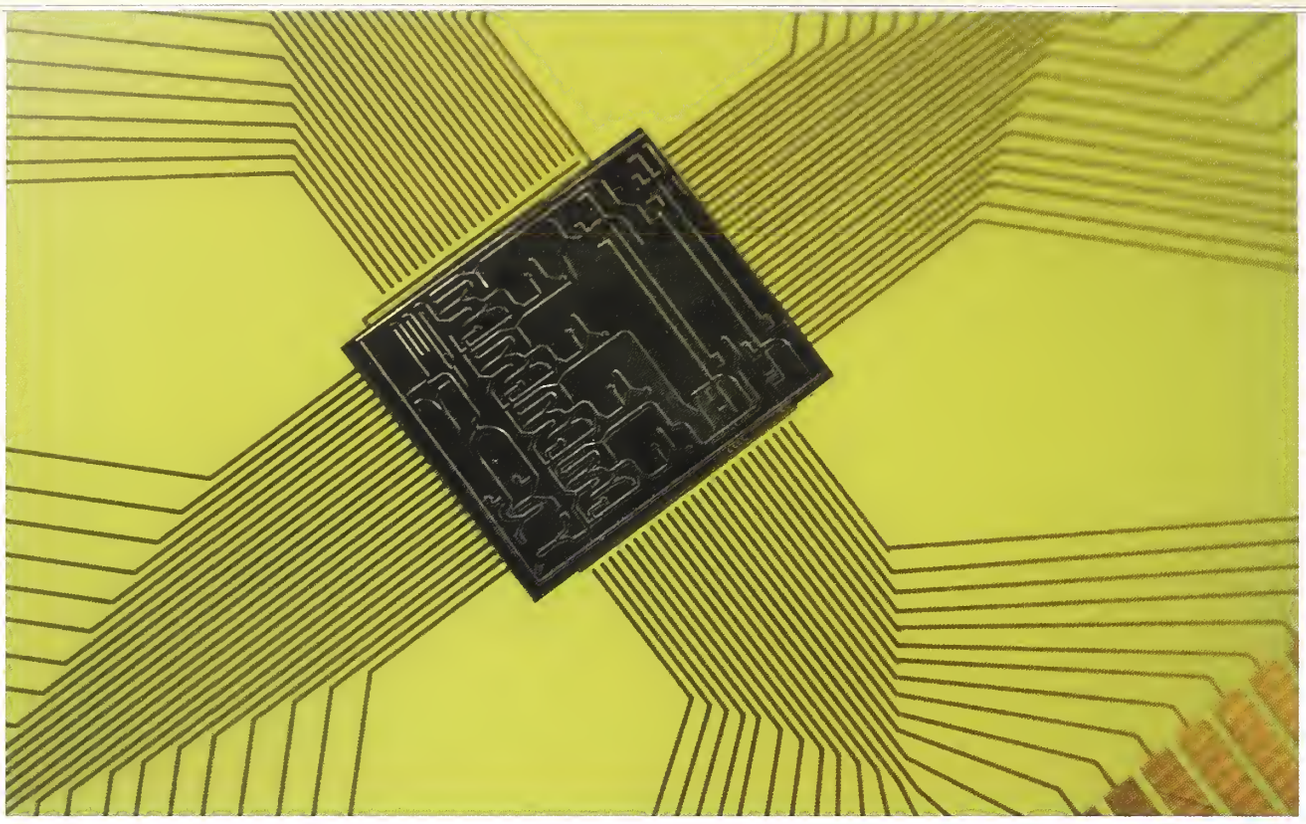
NIH Roadmap for Medical Research

The *NIH Roadmap for Medical Research* is a series of far-reaching initiatives that the NIH will pursue over the next 10 years to reshape the way medical research is done, to have the most profound impact on human health. It was created with extensive input from NIH leadership and more than 300 nationally recognized leaders in academia, industry, government, and the public.

"Through these initiatives, we hope to remove some of the biggest roadblocks that are keeping research findings from reaching the public as swiftly as possible," announced Elias A. Zerhouni, M.D., NIH director, at the September 30, 2003, launch of the *NIH Roadmap*.

➤ The NIH's Rocky Tuan says, "Tissue engineering represents one of the brightest future prospects in medical research." His team of scientists is growing cartilage to repair joints. See page 41.





This microelectromechanical systems chip, sometimes called "lab on a chip," may some day help to provide doctors with on-the-spot DNA diagnostics for a wide range of conditions.

Its three broad themes—New Pathways to Discovery, Research Teams of the Future, and Re-engineering the Clinical Research Enterprise—focus on technologies and systems that will enable researchers to solve problems more quickly and to ask questions that have been unanswerable—questions so complex that without the aid of these efforts, they would be impossible to address. They represent investments that, if made now, will likely yield major payoffs in terms of improved health. Within each theme, implementation groups were made responsible for developing the proposals into tangible activities to be launched in fiscal year 2004 and beyond.

NEW PATHWAYS TO DISCOVERY

When they sequenced the human genome, NIH scientists and their public- and private-sector partners took a historic step in unlocking the complexities of human disease. Now comes the really hard part. This theme, New Pathways to Discovery, addresses the need to understand the complex biological systems that are managed by our genes. It also sets out to build a better "tool box" for today's biomedical researchers. The research community needs wide access to technologies, databases, and other scientific resources that are more sensitive, more robust, and more easily adaptable to researchers' individual needs. The NIH will support screening of libraries of small molecules that can be used as chemical probes to study biological networks and cellular pathways, innovative tools for capturing real-time images of events that take place within the cell, improved computational infrastructure, and tiny, nanotechnology devices capable of viewing and interacting with basic life processes. Nanotechnology research, for example, will help scientists construct miniature implantable pumps for drug delivery or tiny sensors to scan for the presence of infectious agents or metabolic imbalances.

All of the technologies discussed within New Pathways to Discovery will provide the foundation from which new diagnostic, treatment, and prevention strategies will emerge.

Implementation groups in this area are:

- Molecular Libraries and Molecular Imaging
- Bioinformatics and Computational Biology
- Nanomedicine
- Structural Biology
- Building Blocks, Pathways, and Networks

RESEARCH TEAMS OF THE FUTURE

Because of the complexity and scope of today's scientific problems, there has been a fundamental shift in the way science is carried out in this country. Progress is now made by teams, both large and small, that span university departments and disciplines. Medical imaging research, for example, requires cell and molecular biologists, computer programmers, radiologists, and physicists to work together on new diagnostics and treatments. To stimulate new ways of combining skills and disciplines, the NIH is issuing requests for applications (RFAs) to promote collaboration, including Exploratory Centers for Interdisciplinary Research and Training for a New Interdisciplinary Research Workforce.

Scientists must be inspired and encouraged to reach for the potential breakthroughs. The NIH Director's Pioneer Award will encourage investigators to take on creative, unexplored avenues of research that carry relatively high risk but also have the potential to make extraordinary contributions.

Novel partnerships that bring together the public and private sectors will be encouraged to accomplish things that neither could do alone. The NIH will establish a central point of contact to support and encourage activities involving partnerships.

Implementation groups in this area are:

- Interdisciplinary Research
- High-Risk Research—NIH Director's Pioneer Award
- Public-Private Partnerships

RE-ENGINEERING THE CLINICAL RESEARCH ENTERPRISE

Exciting basic science discoveries need to be transformed quickly into preventive measures, diagnostics, drugs, or treatments. This is undoubtedly the most difficult, but most important, challenge identified in the *NIH Roadmap* process.

The NIH will promote the creation of better-integrated networks of academic centers that work together on clinical trials and include community-based practitioners who care for large groups of patients. Realizing this vision will require new ways to organize clinical research data, new standards for research protocols, modern information technology, new models of cooperation between the NIH and patient advocates, and new strategies to re-energize the clinical research workforce.

The NIH must exploit its clinical research investments to learn as much as possible from large trials. A new national clinical research infrastructure would integrate advances in informatics into the medical care setting and provide the capacity to share data among researchers. Such an ambitious national effort would reduce duplication and unnecessary overlap between clinical trials. These endeavors will move forward with special attention to protecting human subjects and safeguarding the

A recently discovered biological phenomenon called RNAi—or RNA interference—has led to the development of a new and potent research tool, which is being used to identify the function of specific genes. For insights into obesity, researchers, with support from the NIH, used RNAi to identify genes involved in fat metabolism in the roundworm, *Caenorhabditis elegans*. One at a time, each of the 17,000 genes of the worm was turned off using RNAi. The researchers found that silencing or inhibiting 305 genes decreased body fat, whereas inhibiting 112 genes increased fat storage. This study identified new genes involved in fat metabolism that are common in many organisms, including humans. Researchers now have many new opportunities for understanding obesity and new targets to develop better treatments.

NIH Roadmap initiatives will be funded by the NIH institutes and centers (0.34% of their total budgets in FY 2004 and 0.63% of their total budgets in FY 2005), and through funds provided by the NIH Director's Discretionary Fund ($35 million in FY 2004 and $60 million in FY 2005). Details of the *NIH Roadmap* are located at *http://nihroadmap.nih.gov.*

privacy of individually identifiable health information.

The clinical research workforce will need to be expanded and supported. Sweeping changes in career development will focus on physician-scientists, as well as each member of the multidisciplinary team, such as the engineer, physicist, nurse, mathematician, statistician, computer scientist, behavioral scientist, pharmacologist, and epidemiologist. The NIH is committed to inspiring young investigators from many disciplines to join the teams needed to conquer illness and disease in this century.

Implementation groups in this area are:

- Harmonization of Clinical Research Regulatory Processes
- Integration of Clinical Research Networks
- Enhance Clinical Research Workforce Training
- Clinical Research Informatics: National Electronic Clinical Trials and Research System (NECTAR)
- Regional Translational Research Centers
- Enabling Technologies for Improved Assessment of Clinical Outcomes

THE NIH TO SIMPLIFY REPORTING OF ADVERSE EVENTS

Clinical investigators should be able to report, with relative ease, an adverse event to the NIH, the Food and Drug Administration (FDA), and any other body that needs to know, such as the study's Institutional Review Board. Until now, no such system existed. The NIH is pilot testing a Web-based system for streamlined reporting of adverse events in clinical trials involving gene transfer.

The NIH recognized that it had to do a better job of collecting reports on adverse events, for example, a drug given during a study that causes an unexpected or life-threatening problem for a patient. The effort was sparked in large part by the tragic death of 18-year-old Jesse Gelsinger during a gene transfer study in 1999. The NIH has designed a system so that reports are easy to submit and can be analyzed appropriately to determine what the event means to the study and the patients, whether it is related to the trial or is a consequence of the trial, or whether the event is part of the patient's disease.

"The system was built to be functional, useful, and interesting, and most important, it will serve the public by protecting their safety and allowing science to move forward," says Lana Skirboll, Ph.D., NIH associate director for science policy.

Skirboll has high hopes for the Web-based system, because it was developed with input from patient groups, clinical investigators, members of the Society for Gene Therapy, and in full collaboration with the FDA. The reports will go into a database so that users can look at the adverse event reports that come in from all trials that report to the Recombinant DNA Advisory Committee, the NIH panel that oversees gene therapy research. Analyses will be done across trials as well, to detect any important trends.

The system is in pilot testing now. The next logical step is to expand the concept to other clinical trials. The NIH is already developing that prototype.

NIH PROFILE

A CAB RIDE TO THE NIH

A conversation in a taxi brought Rocky Tuan to the NIH to grow cartilage.

The best options available today for people with osteoarthritis leave plenty of room for improvement. The most common treatment, total joint replacement, is considered one of the most successful types of surgery available, but artificial joints don't last very long—no more than 10 to 15 years. People in need of new joints are getting younger. A 45-year-old needs a lot more than 15 years of mobility.

Rocky Tuan, Ph.D., is convinced there's a better way, so he's come to the NIH to do studies and train an assortment of scientists in the relatively new field of tissue engineering and regenerative medicine. His team is growing cartilage tissue, building a scaffold on which the cartilage can grow, preparing it to handle the kind of pressures that a weight-bearing joint must handle, and plans eventually to transplant the resulting "bio-implant" into a damaged joint.

When Stephen I. Katz, M.D., Ph.D., director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, decided to launch a program on cartilage regeneration at the NIH, he bent Tuan's ear during a cab ride at an orthopaedics meeting. "That was meant to be a recruitment cab ride," Katz says. "I thought Rocky brought the right balance of outstanding science, a vibrant personality, and passion for making advances in medical science. He's a Ph.D. scientist who thinks clinically and practically."

Tuan, 53, has brought together an eclectic group of scientists at the NIH and has built the kind of research team set out in the *NIH Roadmap for Medical Research.* "The most important requirement is collaborative research among people from different disciplines," he emphasizes. Skeletal tissue is not like blood or other tissues. It needs to carry the body's weight; it requires structural integrity. The cell biologists who can put the cells together need to work with biomaterials engineers to build a scaffold to support the cells. They need a molecular biologist to see if gene-based approaches or growth factors can enhance the regeneration process. Clinicians need to be there with the surgical skills to insert the bio-implants into patients.

Rocky Tuan with [illegible] member [illegible]

Tuan's team has tested bio-implants in miniature pigs with surgically created defective knee joints. "Preliminary data look very promising," Tuan says. Now they are focused on doing laboratory studies with human cells and have succeeded in making what they call an "osteochondral construct"—part bone and part cartilage.

"We used one cell type to create both bone and cartilage," explains Sumon Nandi, a 26-year-old medical student who spent a year in Tuan's lab as part of a one-year training program aimed at attracting medical and dental school students to careers in research. Tuan's lab had already shown that stem cells taken from the top of the thigh bone, called mesenchymal progenitor cells, can be coaxed into becoming cartilage, bone, and fat.

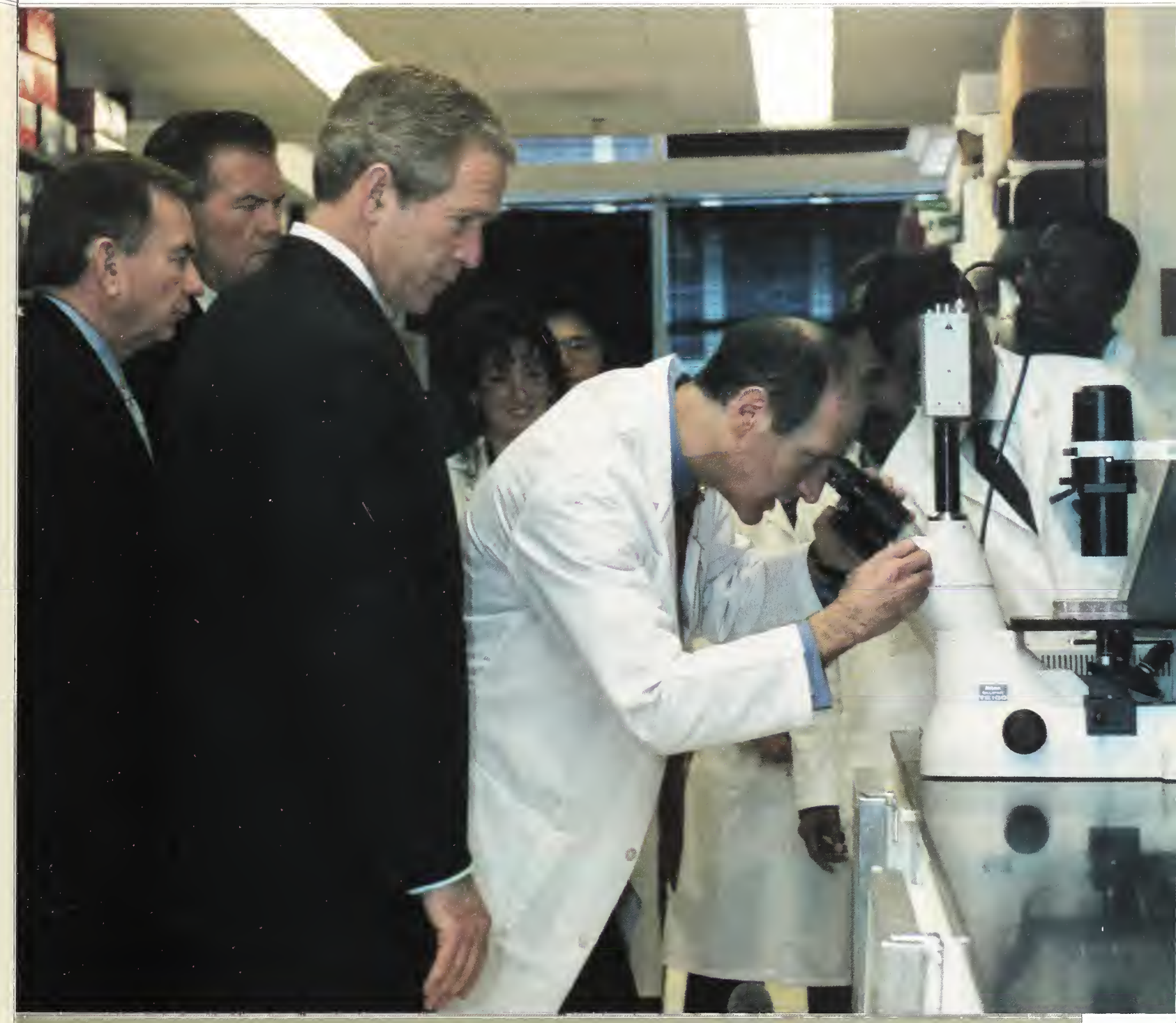
Tuan likens the osteochondral constructs to hair plugs. Ultimately, patients will donate bone marrow or a chip of bone. The stem cells will be harvested and directed to grow into these osteochondral plugs. Surgeons will then transplant a plug into the bone of the damaged joint, where its cartilage end will form a new smooth surface for the joint.

There's still a great deal of work to do before Tuan's team is ready to test cartilage replacement in people. "I'm an optimist, but I'm fully aware of the obstacles," Tuan says. Still, he's convinced there's got to be a longer-term solution for damaged joints, and it's going to have to be a biological one. "In the next decade or two, a truly, totally biological implant can happen."

Defeating Emerging Threats

The NIH is a leader in the fight against today's infectious threats to human health. From its early days as a laboratory for study of infectious diseases to its current, broader mission, it has always been responsive to the public's health needs. Diseases that once killed and disabled tens of thousands of children in the United States—such as measles, whooping cough, and meningitis—are now rare in this country because of vaccines developed with NIH support.

➤ Secretary of Health and Human Services Tommy Thompson, Homeland Security Director Tom Ridge, and President George W. Bush look on as Gary J. Nabel, M.D., Ph.D., director of the NIH's Vaccine Research Center, views anthrax through a microscope.



"Man's efforts to use diseases as weapons of war and terror have placed research scientists at the center of our mission to defend the American people."

—President **George W. Bush** during his February 3, 2003, visit to the NIH campus

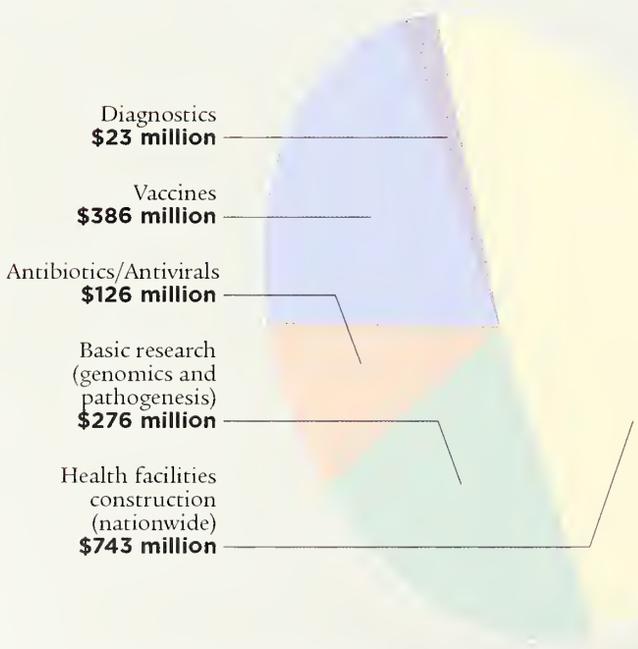
BIODEFENSE—PROTECTING THE PUBLIC

Since the fall of 2001, the NIH, largely through the National Institute of Allergy and Infectious Diseases (NIAID), with support from eight other institutes and centers, has moved quickly to expand, intensify, and accelerate laboratory and clinical research on the prevention, diagnosis, and treatment of diseases caused by potential agents of bioterrorism. NIAID developed more than 50 biodefense initiatives to stimulate research in fiscal years 2002 and 2003. Through these initiatives, NIAID has greatly expanded its support of investigators in academia and partnerships with industry. It also has created new biodefense resources, taken advantage of genomic research advances, and furthered understanding of how microbes cause disease and how the immune system responds to infection.

Initial efforts have focused on the worst bioterror threats, such as viruses that cause smallpox and hemorrhagic fevers such as Ebola; the bacteria that cause anthrax, plague, and tularemia; and botulinum toxin. For fiscal year 2003, the NIH received approximately $1.5 billion for biodefense research. With this strong investment, the NIH has devised a creative research agenda that includes the long-term goal of developing "universal" antibiotics, antivirals, and antitoxins that are effective against all or most classes of biological pathogens.

NIAID is funding the construction of new biosafety laboratories around the country—including one on the NIH campus—to address the serious shortage of such facilities, which are required to safely conduct research on biodefense and emerging infectious diseases. The institute also has funded eight multidisciplinary Regional Centers of Excellence for Biodefense and Emerging Infectious Disease Research and named five Cooperative Centers for Translational Research on Human Immunology and Biodefense. Approximately $85 million spent over 4.5 years will support the latter biodefense research network, focused on the human immune system. Researchers at the cooperative centers will, among other measures, develop new ways to get information from single immune cells, so that very small tissue and blood samples can be tested. Imaging technologies also will be developed to allow non-invasive, real-time views of the body as it reacts to vaccine or infection. The improved techniques could help researchers determine the immune mechanisms responsible for strong versus weak vaccine responses. That information, in turn, will be useful in developing novel vaccines.

BIODEFENSE SPENDING AT THE NIH, FY 2003



The NIH has accelerated its research agenda in biodefense to develop tests to rapidly diagnose, vaccines and immunotherapies to prevent, and drugs and biologics to cure diseases caused by agents of bioterrorism.

"We fully expect that our scientists will develop the tools of diagnosis, treatment, and prevention that will allow us to respond effectively to, and likely deter, future bioterrorist attacks on our citizens," says Anthony S. Fauci, M.D., NIAID director.

ANTHRAX DECODED

In April 2003, NIH-supported researchers announced they had decoded the complete genetic blueprint of the bacterium that causes anthrax and that they had found a number of the genes that help it thrive in its host, providing new drug targets. To date, NIAID has supported sequencing efforts for more than 30 medically important microbes, many of which cause infectious diseases or are potential bioterror agents (see *www.niaid.nih.gov/dmid/genomes*). With precise details about the genetic make-up of these organisms in hand, researchers have the tools to help design effective drugs and vaccines against the diseases the microbes cause.

Doctors believe that SARS can be spread by tiny droplets that become airborne when someone sneezes or coughs. At the height of the SARS outbreak, paper masks became common in several Chinese cities, including Hong Kong and Beijing.

A NEW KILLER

A frightening new disease called SARS (severe acute respiratory syndrome) quickly spread to 30 countries in 2003—most notably shutting down Toronto, Canada, for weeks—and made paper masks the standard fashion in China and Taiwan. It crossed U.S. borders as well. In the first year since it emerged in November 2002, SARS infected 8,100 people and killed about 800.

To spur research on SARS, NIAID is offering free SARS DNA microarray chips to qualified researchers worldwide. This powerful tool will allow researchers to detect tiny genetic variations among different SARS virus strains, and is expected to provide new leads in the search for effective SARS countermeasures. The "SARS chip" is available through a unique partnership between government and industry. Production of the chip is handled by Affymetrix, Inc., of Santa Clara, California. The Institute for Genomic Research in Rockville, Maryland, has a contract with NIAID to provide resources and training for researchers to do functional genomics studies on SARS and other pathogens for which genome sequence information is available.

IT TOUCHED DOWN IN NEW YORK

West Nile virus is spread by insects, usually mosquitoes. It is part of the family of viruses that cause yellow fever and dengue fever. Most human infections are mild, but if the virus reaches the brain, it can cause life-threatening encephalitis (inflammation of the brain) or meningitis (inflammation of the lining of the brain and spinal cord). In 1999, it first appeared in the New York City area. By the summer of 2002, the virus had quickly spread west and south. For 2003, state health departments reported 8,734 cases of West Nile virus, resulting in 208 deaths.

The NIH is supporting research to develop a vaccine, antiviral medicines, and new diagnostic tests for West Nile virus. Knowledge of other viruses has enabled a quick response. For example, NIH work on dengue virus led to a vaccine for West Nile virus that is anticipated to enter testing in humans in 2004.

MOVING TARGETS

Some of the most treacherous disease-causing bugs do their damage because they can adapt to their environments and evade their host's defenses by making rapid genetic changes. But researchers are getting a leg up on how to outwit these

Color-enhanced scanning electron micrograph of spleen tissue from a monkey with inhalation anthrax. Yellow rod-shaped bacilli surround red blood cell.

dangerous microbes by marrying sophisticated mathematical and computer-based approaches to an understanding of the genetics of these organisms. They are learning how to predict and perhaps prevent disease outbreaks—aiming to thwart next year's flu epidemic or fight *Helicobacter pylori*, the bacterium that can cause painful stomach ulcers.

ANCIENT ENEMY, PRESENT THREAT

In a study of tuberculosis (TB), NIH-funded researchers pinpointed a specific gene that allows the tuberculosis bacterium to develop resistance against commonly used antibiotics. The role of the gene was further clarified in mouse studies. Bacteria that lacked the gene did not develop resistance when injected into mice; they responded to common antibiotics. Conversely, mice infected with the normal strain of tuberculosis bacterium died quickly, even when treated with common antibiotics. The TB bacterium currently infects one third of the world's population, and eight million people develop disease symptoms each year. According to the World Health Organization, two million people die from TB annually.

MOVING AGAINST MALARIA

Successful genome sequencing has heralded a new era in the fight against malaria. Genome sequences of *Plasmodium falciparum*, the most lethal malaria-causing parasite, and *Anopheles gambiae*, a mosquito that transmits the parasite to humans, are now complete, thanks to two international research teams funded by the NIH, which announced their results in October 2002. A much fuller understanding of this disease and its transmission is now possible. The medical, social, and economic ravages of malaria are most keenly felt in Africa, where 90 percent of the worldwide death toll from the disease—up to 2.7 million deaths annually—occurs. Most victims are children less than 5 years old; on average, a child succumbs to malaria every 30 seconds.

On the vaccine front, NIAID and an international group of public and private partners have reached a milestone, launching their first trial of a candidate malaria vaccine in a country where malaria is endemic. The phase I trial, taking place in Mali, seeks to confirm that a candidate vaccine called FMP-1 is safe and triggers an immune response in adults. A key component of NIAID's plan for developing a malaria vaccine has been to establish research centers in malaria-endemic areas, including this one in Mali, that can support the complex clinical development of malaria vaccines.

CONTAINING EBOLA OUTBREAKS

It is the stuff of movies. The Ebola virus wreaks havoc so swift and deadly, it often kills the patients and the health care workers around them. Since 1976, more than a dozen outbreaks have killed hundreds in central Africa. In November 2003, the world's first human clinical trial of an Ebola vaccine opened at the NIH. The vaccine being tested was designed by scientists at the NIAID Dale and Betty Bumpers Vaccine Research Center. Because there is no treatment for the disease, preventing the spread of the virus is critical to containing outbreaks.

NIH PROFILE

ANTHONY S. FAUCI

Anthony S. Fauci, M.D., has been involved in the fight against HIV/AIDS since he read a report in 1981 in the Centers for Disease Control's *Morbidity and Mortality Weekly Report* on cases of a strange infectious disease affecting gay men. By the year's end, he had turned his lab into a research center for the disease that later became known as AIDS. Fauci has been director of the National Institute of Allergy and Infectious Diseases since 1984, in charge of the nation's research agenda on HIV/AIDS as well as other infectious diseases. The institute has made great progress in understanding how HIV infects the body, including Fauci's 1993 study that showed HIV infection is never latent in the body, but always lurking in the lymph nodes. NIAID-supported researchers have developed a battery of drugs to hold the disease at bay and prolong life. Still, progress has not come as quickly as Fauci would like. "We still have a major problem with developing a vaccine," he says. "It's a problem that can be overcome, but, as in all complicated problems in biomedical research, it's going to take time." Fauci also oversees the NIH's expanding biodefense research agenda.

Recent notable achievements from NIH-funded research

A Time of Discoveries

➤ Special cells reveal heart disease risk in men.

By measuring the amount of a special type of cell in the blood—endothelial progenitor cells—researchers supported by the National Heart, Lung, and Blood Institute were able to determine heart disease risk in a small group of men. These cells, generated in the bone marrow, carry out a critical function for the heart by repairing damaged blood vessel walls. Men with fewer endothelial progenitor cells had a higher risk for heart disease. The results need to be confirmed in larger studies.

➤ 3-D pictures expose cause of Lou Gehrig's disease.

Using an imaging technique called x-ray crystallography, researchers supported by the National Institute of Neurological Disorders and Stroke were able to observe the behavior of proteins involved in an inherited form of amyotrophic lateral sclerosis (ALS), better known as Lou Gehrig's disease. The images showed that proteins that are mutated in ALS lack a loop-shaped structure found on the normal proteins. Further study showed that the loop is essential to blocking the aggregation of proteins, an accumulation that damages the nervous system.

➤ Protein screen for Alzheimer's disease is promising.

By measuring two proteins in cerebrospinal fluid, researchers at the National Institute of Mental Health found that, with high sensitivity, they could distinguish patients with Alzheimer's disease from healthy individuals. The hope is that these disease indicators will be able to identify young people who have Alzheimer's with no outward symptoms. Such early diagnosis might some day allow doctors to begin early treatment for the disease before considerable damage to the brain occurs.

➤ Clues revealed to pregnancy problems.

Using biopsies of uterus linings, researchers have determined how a human embryo initially attaches to the wall of the uterus—one of the earliest steps needed for a successful pregnancy. The discovery may provide insights into infertility and early pregnancy loss. Findings may also offer insight into preeclampsia, a life-threatening high blood pressure that develops in pregnancy and appears to result from failure to establish the blood vessels connecting the embryo to the mother's blood supply. The study received funding from the National Institute of Child Health and Human Development, National Institute of General Medical Sciences, National Heart, Lung, and Blood Institute, and National Institute of Dental and Craniofacial Research.

➤ Coenzyme Q10 slows disease in early-stage Parkinson's.

Results of a small clinical trial of the compound known as coenzyme Q10 suggest that it can slow disease progression in patients with early-stage Parkinson's disease by improving production of energy in the cell. Larger clinical studies are under way to determine if Q10 can offer a new way of treating Parkinson's disease. The study was supported by the National Institute of Neurological Disorders and Stroke.

➤ Pets protect against allergies.

Children reared with two or more dogs or cats during the first year of life may be protected from ever developing allergies, according to a study supported by the National Institute of Allergy and Infectious Diseases and the National Institute of Environmental Health Sciences. The animals appear to protect against more than pet allergy, but also dust mite, ragweed, and grass allergies.

FOR MORE DISCOVERIES, SEE PAGES 13 AND 23.

Today's Big Challenges

True, Americans are living longer and reaping the benefits of medical research. With those added years, however, come new challenges. Chronic and long-term conditions—congestive heart failure, cancer, Alzheimer's disease, Parkinson's disease, diabetes, and obesity—are on the rise. The NIH is facing these challenges with a strong research agenda and innovative outreach programs.

➤ Gary H. Gibbons, Morehouse School of Medicine, is working at the interface between laboratory research and medical care to prevent stroke and kidney failure. See page 52.

OBESITY RATES ARE OUT OF CONTROL

Almost two of every three American adults are overweight or obese, and the prevalence is increasing. Rates are higher in underserved minority populations. The percentage of overweight children has tripled over the past three decades. People who are overweight or obese are at risk for a wide spectrum of deadly ailments—type 2 diabetes, heart disease, hypertension, stroke, cancer, and asthma, among others.

The NIH is developing strategies to help children achieve and maintain healthy weight through increased activity and healthier diet.

The NIH takes this challenge seriously and has developed a broad research agenda with three major goals. Some NIH-supported researchers aim to find and disseminate strategies to maintain healthy weight in children and adults through behavior change—increased activity, healthier diet—that can be applied in home, school, or workplace environments. Others are working to use new knowledge of energy regulation to develop better treatments—drugs, surgery, and other technologies—to complement behavior interventions. Finally, scientists are developing potential treatments to ameliorate the serious consequences of obesity regardless of weight loss.

The NIH supports studies that span the research spectrum from genetic studies, to clinical studies of approaches to help people keep the pounds off, to outreach campaigns aimed at persuading Americans to get moving.

- **Get Out, Get Active.** Hearts N' Parks is a community-based program, supported by the National Heart, Lung, and Blood Institute (NHLBI) and the National Recreation and Park Association, to provide science-based information about favorable lifestyle choices and teach skills for incorporating heart-healthy behaviors. More than 50 Hearts N' Parks sites are active in 11 states throughout the country. Results show that after participating, children, teens, and adults reported adopting healthier behaviors, and adults reported an increase in their level of regular physical activity (see *www.nhlbi.nih.gov/health/prof/heart/obesity/hrt_n_pk/index.htm*).

- **Keep It Off.** NHLBI has launched a major study that could help solve one of the toughest aspects of weight loss—keeping the lost pounds from creeping back. Phase I of the Weight Loss Maintenance Trial will include 1,600 men and women in a five-month weight loss program. In phase II, 800 of those who lost nine pounds or more in phase I will go through an intervention to keep the weight off for 2½ years. About 60 percent of participants will be women, 40 percent will be African American.

- **Listen to Your Gut.** Ghrelin is a gut hormone getting lots of attention for its role in stimulating appetite. In one study supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in response to a weight loss of 17 percent, ghrelin levels increased by 24 percent—the body's way of compensating to maintain energy balance. In contrast, PYY3-36 is another gut hormone that appears to inhibit hunger pangs. With injections of the hormone, people ate less. Because appetite control is such a challenge for dieters, understanding the activities of ghrelin and PYY3-36 may prove important for helping dieters achieve and sustain weight loss.

- **Improving Community Design.** The National Institute of Environmental Health Sciences is studying strategies to

change eating behavior, promote a more active lifestyle, and change the design of residential communities to make them more conducive to walking. The institute is partnering with other federal agencies, such as the Department of Housing and Urban Development, to develop and test strategies and economic incentives to promote lifestyle change and reverse Americans' weight gain.

EPIDEMIC OF TYPE 2 DIABETES SWEEPS THE UNITED STATES

More than 18 million Americans have diabetes; of these, 5.2 million have the disease but don't know it. Moreover, another 20 million Americans have prediabetes—a condition in which blood sugar levels are higher than normal but not diabetic. Type 2 diabetes, in which the body becomes resistant to insulin, is the most common form of the disease. Rates of diabetes have increased steadily since 1980—along with rates of obesity, a serious risk factor for type 2 diabetes. By 2020, the number of people with diabetes is expected to double. Diabetes is the leading cause of adult blindness, kidney failure, and limb amputation, and is a major cause of premature heart disease and stroke.

Because type 2 diabetes in children is growing at an alarming rate, the NIH is supporting studies to develop school-based interventions to prevent diabetes risk factors. It is also supporting a clinical trial to determine how best to treat type 2 diabetes in children. In adults, the NIH is supporting a follow-up study of participants in a landmark clinical trial, the Diabetes Prevention Program, which, over several years, successfully used intensive lifestyle interventions (see page 72) or the drug metformin to delay or prevent type 2 diabetes in those at high risk for the disease, including minority adults. Researchers are now assessing the longer-term benefits of these treatments in preventing type 2 diabetes and its complications.

DISEASES THAT DERAIL HEALTHY AGING

Alzheimer's Disease The number of people who experience the frightening memory loss, disorientation, and behavior changes of Alzheimer's disease is projected to quadruple in the next 50 years. Some 13.2 million older Americans will have Alzheimer's disease by 2050 unless new ways are found to prevent or treat the disease. According to these latest estimates by researchers at Rush-Presbyterian-St. Luke's Medical Center in Chicago, the number of older people with Alzheimer's—now at 4.5 million—will grow dramatically as the population ages. The most notable increases will be among people age 85 or older; by mid-century eight million people in that age group may have the disease.

No prevention or cure is available yet, but research into the causes and progression of Alzheimer's disease is moving ahead at a fast pace. The three major genes for early-onset Alzheimer's and one of the major risk factor genes for late-onset Alzheimer's have been identified. Scientists now know a lot about the pathways that lead to the development of "plaques" in the brain—one of the main features of Alzheimer's disease. The NIH is funding clinical trials to look at ways to prevent Alzheimer's, identifying individuals at high risk through imaging, neuropsychological tests, and structured interviews.

To learn what the NIH is doing about Alzheimer's, visit the National Institute on Aging's special Web site at *www.alzheimers.org* or contact the institute's Alzheimer's Disease Education and Referral (ADEAR) Center at 1 (800) 438-4380.

Parkinson's Disease Up to 600,000 Americans are living with Parkinson's disease, and that number is expected to grow to 1.3 million by 2040. The tremors and rigidity that are the hallmarks of this progressive disease of certain brain cells are more likely to occur in people over age 60. The NIH has an aggressive research agenda, targeting every major avenue of Parkinson's

Major genes involved in Alzheimer's disease and Parkinson's disease have been identified in recent years.

NIH PROFILE

PUTTING SCIENCE TO SERVICE

Gary Gibbons is giving back by helping African Americans with heart disease.

Why do some people with hypertension have a stroke and some don't? Why kidney failure for some and not others? Gary H. Gibbons, M.D., a cardiologist who directs NIH-funded research at the Morehouse School of Medicine in Atlanta, aims to find out. He has the tools to answer those questions and help African Americans and other minority groups whose hypertension is more likely to lead to stroke and kidney failure.

"What is it about the way vessels are structured or how they function that predisposes the patient to complications?" Gibbons asks. He's looking at the genes involved in blood vessel formation and function to see which are turned on or off in illness. He has begun a study in humans, using biopsies of fat tissue from the buttocks. The fat is full of blood vessels, Gibbons says, and when blood vessels in the body narrow, as in hypertension, all of the body's vessels narrow, even those in the fat. So the fat biopsies are a relatively easy way to search for genes involved in the changes that occur with hypertension. His tools are microarray technology and SAGE (serial analysis of gene expression), which can give an accounting of all messages within a cell or tissue.

Gibbons envisions being able to find new targets for treatment to avoid stroke and renal failure, or predict which people with hypertension are at greatest risk for complications so they can be treated appropriately. Real predictive medicine isn't here yet, he says, "but it's why we do what we do."

Gibbons is director of the Morehouse Cardiovascular Research Institute, an NIH/NHLBI-sponsored Research Center of Excellence. He's also a key investigator in the Stroke Prevention and Intervention Research Program at Morehouse, funded by the National Institute of Neurological Disorders and Stroke, National Center for Research Resources, National Center on Minority Health and Health Disparities, and NHLBI. A clinician-scientist, he's a doctor who works at the interface of patient care and laboratory research. As Gibbons puts it, "We couldn't do what we do today without fundamental advances. But it's critical they get to the front lines." Clinician-scientists help to bridge the gap between laboratory research and medical care. The NIH, among others, is designing training programs to increase the number of clinician-scientists in the field.

Before joining Morehouse in 1999, 47-year-old Gibbons was a faculty member at Harvard Medical School. He says he made the switch for two reasons: to train minority students and to bring the very best of research to the minority community that Morehouse serves. "If one wants to make an impact, go to the front lines. That's where you get insights, test hypotheses, see what works and what makes a difference," he says.

"I feel particularly obligated to the next generation of minority students," says Gibbons. Morehouse is where the minority students are, he says, and "the students need role models doing top science."

research—genetics, environmental factors, drugs, deep brain stimulation, gene therapy, and stem cell research. Exciting new avenues of research opened up in 1996, when changes in a gene called *a-synuclein* were identified in a few large families in whom the disease was unusually common. Since then, research supported by the National Institute of Neurological Disorders and Stroke has identified changes, or mutations, in several other major genes thought to be responsible for Parkinson's disease. The National Institute of Environmental Health Sciences (NIEHS) is supporting research to identify environmental triggers of this disease and explore gene-environment interactions. NIEHS is developing a Parkinson's Disease Consortium to provide a formal mechanism for communication among clinicians, basic research scientists, and patient advocates involved in the disease. To learn more about the NIH's research on Parkinson's disease, visit *www.ninds.nih.gov/parkinsonsweb/index.htm* and *www.niehs.nih.gov/oc/factsheets/parkinson/home.htm*.

THE CHALLENGE OF CANCER

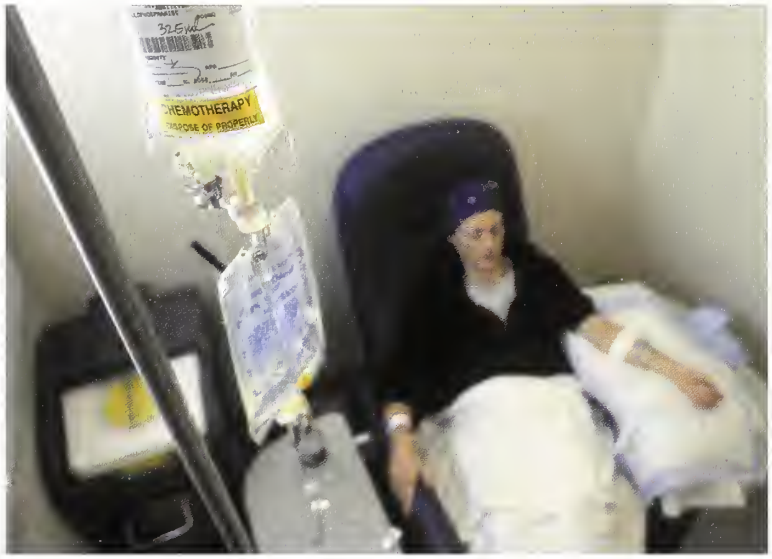
With the progress researchers have made toward eliminating the suffering and death caused by cancer, the disease is no longer the automatic death sentence it once was. More people are living with cancer as improved diagnosis and treatment transform this disease into a more manageable, chronic condition. Death rates from the four most common cancers—lung, breast, prostate, and colorectal—continued declining in the late 1990s. Cancer incidence rates for all types of cancers increased from the mid-1970s through 1992, declined from 1992 to 1995, and then stabilized from 1995 to 2000.

- There are more breast cancer survivors than ever before. Several drugs developed and/or tested by NIH-supported scientists have proven effective in treating, or sometimes preventing, certain types of breast cancer. Tamoxifen, letrozole, and Herceptin (trastuzumab) have all helped treat or prevent breast cancer and are being evaluated in combination with different drugs or in different populations of women.

- For colorectal cancer, death rates have dropped by 25 percent since the 1970s. Incidence of the disease declined from 1985 to 1995 but has since held constant. Again, more people are living with this disease. Drugs have been shown to be effective against recurrence, calcium supplements may reduce risk, and more sensitive tests for the disease are being developed. NIH-supported researchers are working with state, local, and private-sector partners to bring colorectal cancer screening to all segments of the population.

LIVING IN THE DARK

Age-related macular degeneration (AMD) is a major cause of blindness, affecting 1.75 million Americans. More than seven million individuals are at substantial risk for developing AMD, and risk increases with age. By the year 2020, the number of people with AMD will increase to almost three million. A major NIH study showed that high doses of vitamin C, vitamin E, beta-carotene, and zinc could lower by 25 percent the risk that age-related macular degeneration will advance—news that could help 66,000 people per year avoid further vision loss. The NIH plans to spread the word of this discovery to change medical practice and has a strong research program to understand the predisposing factors and genes that control the risk of this devastating disease, and develop more interventions to prevent or delay the onset of blindness.



New treatments are transforming cancer into a more manageable, chronic disease. Death rates are dropping.

IT SHOULDN'T HURT TO WALK

Arthritis is a common and costly condition. An estimated 43 million Americans have some form of arthritis or other

rheumatic condition (characterized by redness, swelling, pain, and loss of function of a joint or other supporting structure of the body). By the year 2020, that number is expected to climb to 60 million, or more than 18 percent of Americans, largely due to the aging of the population. The cost of treatment plus indirect costs of lost productivity are huge, as high as $124.8 billion per year. The most common form of arthritis is osteoarthritis, a degenerative joint disease in which cartilage, the slippery tissue that covers the ends of bones in a joint, wears away. This allows bones under the cartilage to rub together, causing pain, swelling, and loss of motion of the joint. Osteoarthritis is one of the most frequent causes of physical disability among adults. It occurs mostly in older people but can also affect younger men and women. Rheumatoid arthritis—an autoimmune disease in which the body rejects its own tissue and causes swelling of the lining of the joints, with accompanying pain and stiffness—affects approximately 2.1 million Americans.

THE BURDENS ARE NOT FELT EQUALLY

African Americans, Hispanics, American Indians, Alaska Natives, and Asians and Pacific Islanders—the fastest growing communities in this country—and the urban and rural poor continue to suffer an unequal burden of death, disability, and disease, despite improvements in the overall health of the U.S. population over the past decade. Elimination of health disparities is a top priority for the NIH.

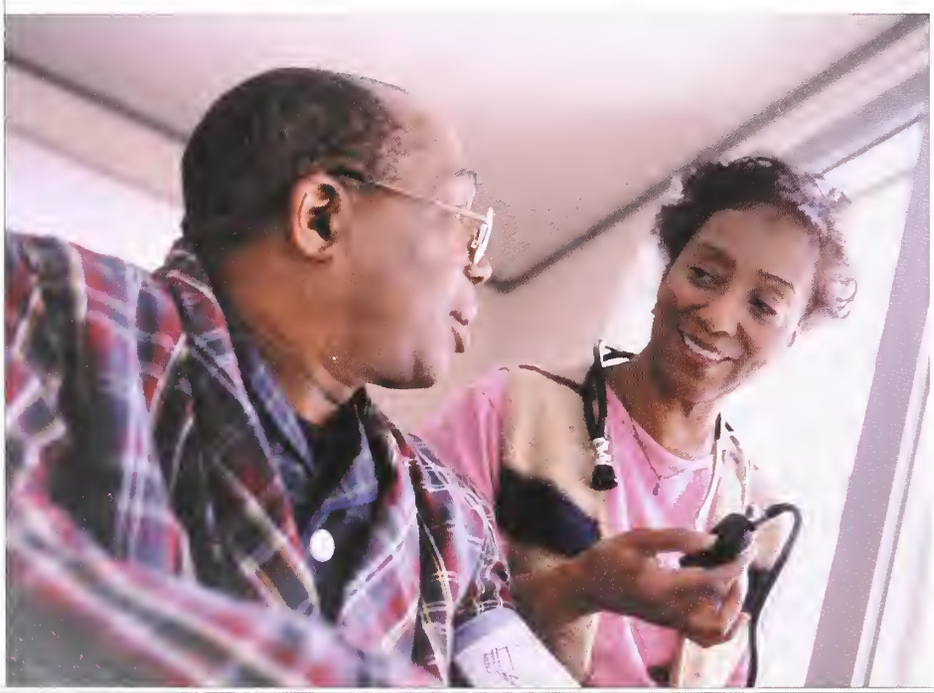
The NIH has developed a strategic research plan to reduce and ultimately eliminate health disparities. Created with strong community input, it has three main components: research, research infrastructure, and community outreach. It includes plans to address the health disparities, build a cadre of biomedical and behavioral investigators who are skilled at working with diverse cultures, and increase the number of minority clinical and basic medical scientists.

The NIH's National Center on Minority Health and Health Disparities (NCMHD) works with other institutes to support research and programs to reduce health disparities. In October 2003, the Department of Health and Human Services announced a $65 million award to NCMHD to increase research aimed at eliminating health disparities among racial and ethnic minority and medically underserved communities.

- In East Baltimore's inner city, a group of young African-American men gained control of their high blood pressure, thanks to a comprehensive intervention conducted at the community level by a multidisciplinary health care team. After three years, forty-four percent of the men receiving the intensive form of the intervention attained control, compared with only 17 percent at the study's start. The study was funded by the National Institute of Nursing Research.

- Depression treatments, for the first time, were found effective for young, low-income African-American and Latina women despite the stresses in their lives, according to a study funded by the National Institute of Mental Health.

- June 2003 marked NIDDK's launch of the first pilot education program to increase awareness about prevention of kidney failure and promote early testing among African Americans, who are the hardest hit. The National Kidney Disease Education Program began a year-long program in four cities—Atlanta, Baltimore, Cleveland, and Jackson, Mississippi—chosen for their relatively large African-American communities and because some resources already existed to develop coalitions in each city.



The NIH's strategic plan to reduce health disparities includes increasing the number of minority clinical and basic medical scientists.

LIKE DEATH AND TAXES?

Cynthia Kenyon debunks the notion that aging is inevitable.

The average roundworm, called *C. elegans*, lives about 21 days. Manipulate a single gene, and its lifespan jumps to 45 days. Toy with its reproductive cells as well, and it will live four times longer than normal. Similar age-enhancing effects can be seen when the same genes are changed in fruit flies and mice.

But what can these odd animals tell us about the way humans age? "Lots," says biochemist Cynthia Kenyon, Ph.D. Animals might look very different, but at a basic level, things are very similar. "All animals are made of cells. Muscle and nerve and intestinal cells are incredibly similar between people and any of the animals we use as model organisms in science." The muscle fibers of the tiny worm look the same as ours. The genes that plan how the body develops are similar as well.

"It's a little bit humbling to realize how similar we are to primitive, simple animals," admits Kenyon, a 50-year-old professor of biochemistry at the University of California at San Francisco. "But that's the way it is."

It makes Kenyon's research enthralling. With support from the National Institute on Aging, her team discovered 10 years ago that a single change in the *DAF2* (decay accelerating factor) gene, which encodes a receptor similar to the human receptors for the hormones insulin and IGF-1, doubled the worms' lifespan. Because the same pathways have been shown to affect lifespan in fruit flies and mice, it's possible that they affect lifespan in humans as well.

The striking thing is that the gene mutation doesn't just delay aging, it postpones the diseases of aging as well. In 2002, Richard Morimoto's team at Northwestern University changed the *DAF2* gene in a strain of *C. elegans* that develops Huntington's disease. The worms got Huntington's, but later. Same for mice: they get cancer, but not until they're older. Kenyon's lab went on to show that this occurred because *DAF2* controls other genes that prevent abnormal proteins, like the Huntington's protein, from clumping together—the hallmark of this disease.

In June 2003, the researchers reported results using DNA microarray technology to trace all the genetic changes that flow from that single *DAF2* change. They found that *DAF2* exerts its influence through genes that fight infection and control metabolism, through genes that control the cell's response to stress, and by dampening the activity of specific genes that shorten life. In short, *DAF2* turns up expression of many different genes, each of which helps out in its own way.

"The consequences are stunning," Kenyon says, "and if we can figure out a way to copy these effects in humans, we might all be able to live very healthy long lives."

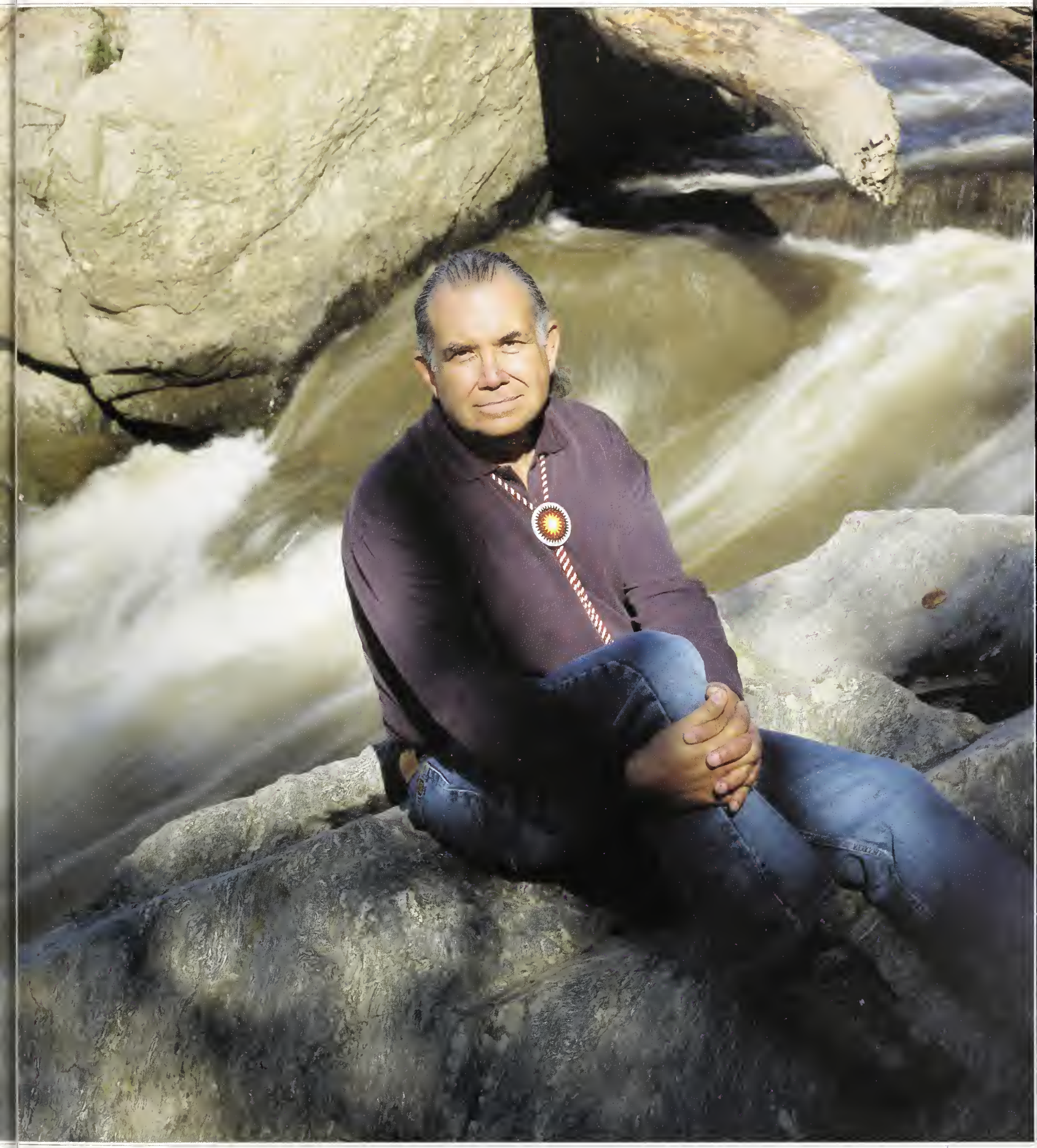
She says looking at these longer-living worms is exactly like looking at a 90-year-old who is indistinguishable from a 45-year-old in every way. That motivated her to launch a company called Elixir to develop and find drugs that can have the same impact and get them to market. "It's a wonderful thing that society has done—created a fabulous basic research operation and then a complementary biotech industry that moves the basic research to the clinic," she marvels.

"I'm not saying there will be a pill to double lifespan immediately," she warns. "But if it worked in worms and now other animals, we're faced with possibilities we never saw before." The drugs that eventually succeed, she predicts, will be those that affect the diseases of aging. "Many people might question whether we want to expand lifespan, but there's no question about staying healthy and avoiding diseases."

Leadership of a Dynamic Community

The NIH was born on Staten Island, New York, in 1887 with another name and a narrow mission—to conduct research on infectious diseases. The modern NIH took shape shortly after World War II, when supporting health research became a focus for public and congressional enthusiasm and funding. Throughout the 20th and now 21st centuries, the NIH has been setting the agenda for medical research for the country and the world.

➤ People should get involved with the NIH, says Ted Mala, Alaska Native Medical Center in Anchorage and a member of the NIH Council of Public Representatives. See page 61.



Using an ABI 100 DNA sequencer, biologist Liz Gillanders, NHGRI, does genotyping for large-scale genetic mapping studies.

HOW THE RESEARCH HAPPENS

About 10 percent of the NIH budget funds the intramural research program, conducted by about 6,000 researchers on the Bethesda, Maryland, campus and at facilities in Research Triangle Park, North Carolina; Baltimore and Frederick, Maryland; Hamilton, Montana; and Phoenix, Arizona. Slightly more than 80 percent of the NIH budget supports the extramural research program. By launching the extramural program in 1946, the NIH firmly established the importance of enlisting scientists at the nation's medical schools and universities in the national research effort to understand disease and health. Today, about 212,000 research grant recipients, fellows, and trainees at institutions across the country have NIH grants to do medical research.

The NIH supports salaries of the scientists and technicians; cost of equipment, such as lasers, sophisticated microscopes, and computers; supplies, such as chemicals and test tubes; and procedures conducted with patients in clinical studies. It also compensates the institutions where research is conducted for maintenance of facilities and administration of grants.

Most of the NIH-supported extramural research is funded through grants to investigators who submit an idea deemed worthy in peer review. These grants are called investigator-initiated research. Sometimes the NIH solicits research applications if an institute is convinced that a particular area of science offers opportunity but scientists are not generating research proposals in that area, or if an institute wants to encourage scientists to apply their skills to a new challenge. Research project grants can fall anywhere along the continuum of medical research—from molecular and cellular studies to clinical studies of new drugs to treat human illness. In fiscal year 2003, the NIH funded approximately 36,000 research project grants. The NIH also awards research and development contracts to non-profit and commercial organizations for work requested and overseen by NIH staff. For example, the drug Taxol (paclitaxel), used to treat breast and ovarian cancer, resulted from NIH contracts aimed at producing a synthetic version of the active ingredient that had been purified originally from bark of the Pacific yew

tree. The company established a factory to produce paclitaxel, so that it was no longer necessary to cut down slow-growing yew trees and to overcome drug shortages.

The NIH uses peer review groups of independent experts—predominantly non-government scientists—to identify and fund the most promising research proposals. Applications are first reviewed for scientific merit by peer review panels called study sections. There are about 172 study sections, which normally meet three times per year to review grant applications. The merit of a research proposal is assessed based on the importance of the problem or question; the innovation employed in approaching the problem; the adequacy of the methodology proposed; the qualifications and experience of the investigator; and the scientific environment in which the work will be done. Applications are then reviewed by the appropriate NIH institute or center advisory council, which evaluates them for relevance to established goals and public health needs. Slightly more than one in three grant applications the NIH receives is funded. Projects by scientists on the NIH campus are also peer reviewed by groups called Boards of Scientific Counselors, consisting of scientific experts chosen mainly from outside the government. The highest-rated projects form the backbone of the science funded by the NIH.

Research takes time. NIH grants are awarded for an average of four years. In any given year, only about 25 percent of the total funds available for research projects goes to funding new projects.

DIVERSITY WORKS

In October 2003, NIH Director Elias Zerhouni accepted on behalf of the NIH the Leadership Award from Diversity Best Practices. "If we are to uphold our reputation for excellence, each and every employee must work together to make the NIH the employer of choice." In his Senate confirmation hearings, Zerhouni also stated, "We need to continue to train, recruit, and retain the best talent in biomedical research because, in the final analysis, it is always the creative spark of the unique individual that leads to new knowledge and real progress." The NIH's policies and management promote the principles of inclusion. Equal opportunity at the NIH promotes excellence in biomedical research. Recruitment, retention, and training activities, including several student programs at the NIH, all work to establish a medical research workforce that represents all segments of society. Diversity is critical because disease knows no boundaries, and NIH-supported research is for the benefit of all populations.

Cecil B. Pickett, Ph.D., president of the Schering-Plough Research Institute, is a member of the Advisory Committee to the Director of NIH.

THE BEST AND THE BRIGHTEST

More than 100 NIH grantees have won Nobel Prizes, the highest honor bestowed in medical research. Martin Rodbell, Ph.D., who was an NIH intramural researcher, is one of five exceptional intramural scientists to win this top recognition. In a series of pioneering experiments conducted at the NIH, Rodbell and his colleagues discovered a mechanism that transformed our understanding of how cells respond to signals. They studied hormones, substances that have specific effects on cells' activities. His results explained not only how hormones function but also how light and odors are perceived, how signals travel between neurons in the brain, and how some diseases affect the body. In 1994, the Nobel Prize in Medicine was awarded jointly to Rodbell and long-time NIH grantee Alfred G. Gilman, M.D., Ph.D., of the University of Texas Southwestern Medical Center, for the discovery of G-proteins and their role in signal transduction in cells. Because they are proteins that bind the nucleotide GTP, Gilman called them G-proteins. The NIH's Stetten Museum of Medical Research has composed a virtual exhibit describing the broad impact of Martin Rodbell's 40-year career at the NIH: *http://history.nih.gov/exhibits/rodbell/index.htm.*

A SEAT AT THE TABLE

The public has a large stake in the success of NIH efforts, and so citizen participation in NIH planning and activities is sought often, through formal advisory committees and ad hoc groups. Citizens from patient communities and underserved communities join scientists and health care professionals in setting the nation's medical research agenda.

The Advisory Committee to the Director of NIH includes members from academic institu-

tions, private industry, and organizations that support scientific research. They meet with the NIH director twice a year to provide feedback on policy matters pertinent to NIH mission responsibilities in the conduct and support of medical research, science, and communications. The committee may make recommendations about program development, resource allocation, NIH administrative regulation and policy, and other specific or general aspects of NIH policy.

The NIH director also receives input through the Council of Public Representatives, or COPR (pronounced "copper"). The 20-member council is composed of diverse members of the public, including patients, family members of patients, health care professionals, scientists, health and science communicators, and educators. This federal advisory committee, formed in 1998, is an important avenue for representatives of the public to advise the NIH director on the broader public perspective on emerging health and science priorities. In addition, COPR members serve as NIH ambassadors by taking information from the NIH back to the broader public (see profile of Ted Mala, page 61).

Each institute relies on public input as well, for example:

■ **Workshops on Genetic Research with Native American Tribes and with Hispanic and African-American Communities**, *National Institute of General Medical Sciences (NIGMS)*
The First Community Consultation on the Responsible Collection and Use of Samples for Genetic Research was held in Bethesda, Maryland, and in follow-up, NIGMS and eight other NIH components co-funded a small workshop, organized by Native American tribes. These workshops focused on the need to educate the public about genetic research, involve communities in all phases of a study, and develop respectful ways of interaction between researchers and communities (see *www.nigms.nih.gov/news/reports/community_consultation.html).*

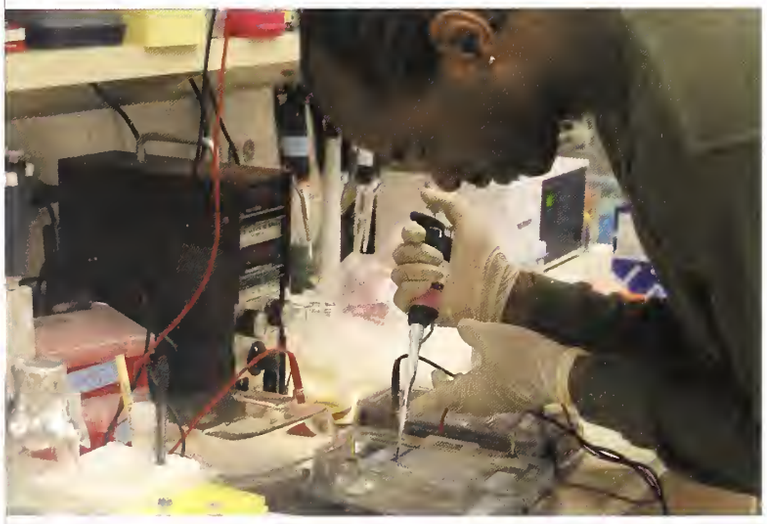
■ **The Jackson Heart Study**, *National Heart, Lung, and Blood Institute (NHLBI)*
NHLBI and the National Center on Minority Health and Health Disparities are co-funding the Jackson Heart Study—research on the environmental and genetic factors influencing development of cardiovascular disease in African-American men and women. Through community mobilization efforts, the Jackson Heart Study has involved many different community groups (media, education, business, health organizations, health care providers, religious organizations, and neighborhood associations) to encourage participation in the study and to provide general health education to the community.

■ **National HIV Vaccine Communications Steering Group**, *National Institute of Allergy and Infectious Diseases (NIAID)*
The steering group was established to increase awareness in racial and ethnic minority communities and among the general public of the need for HIV vaccine research and to create an environment that will be supportive of participation in HIV vaccine clinical trials. Composed of individuals from diverse communities, the steering group includes recognized leaders in communications, the media, social marketing, community education, health care, HIV advocacy, and public policy.

■ **Listserv**, *National Institute of Child Health and Human Development (NICHD)*
For more than two years, NICHD has maintained a listserv to reach its many constituencies. Divided into 10 main categories, specific listserv notices are sent on a regular basis with announcements of recently issued RFAs, press releases and public statements from the NICHD director, and requests for input in strategic planning. The listserv reaches more than 1,500 researchers and research advocates nationwide.

■ **Director's Consumer Liaison Group and Consumer Advocates in Research and Related Activities**, *National Cancer Institute (NCI)*
Since 1997, a panel of 15 consumer advocates has advised the NCI director through participation on the all-consumer advisory board, the Director's Consumer Liaison Group

Milton English, research fellow at the National Human Genome Research Institute.



A PUBLIC VOICE AT THE NIH

Ted Mala speaks out about health disparities. He encourages others to do the same.

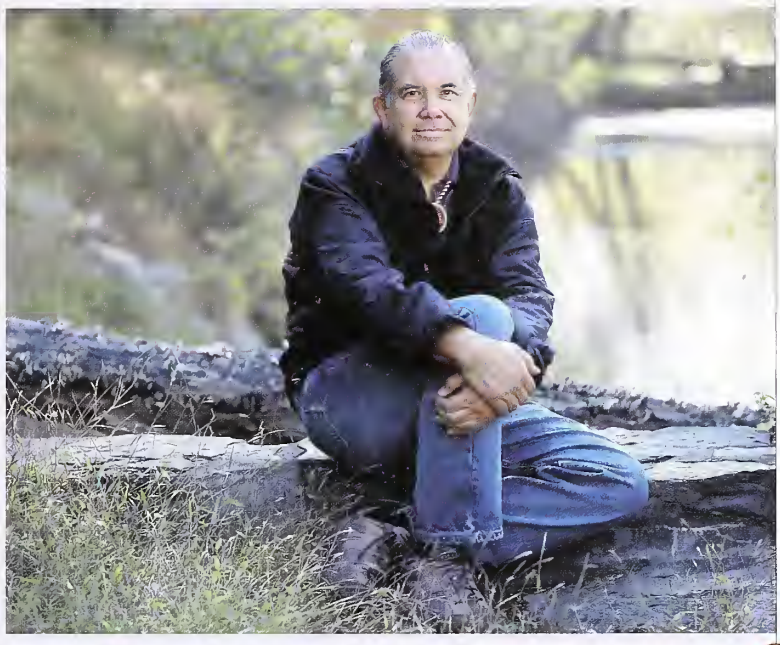
Ted Mala, M.D., M.P.H., is from a family of traditional healers in a small village called Buckland, Alaska, with a population of 500, no roads, no running water, and no piped sanitation. When he was 6 years old, Mala lost his father to mitral valve heart disease—a result of a childhood bout with rheumatic fever, a very big problem in Alaska at the time. He saw his aunts succumb to tuberculosis.

Today Mala, 58, is a physician and director of tribal relations at the Alaska Native Medical Center in Anchorage. He travels the globe to improve health care for Alaska Natives and other minorities. Since 2002, he's been a member of the NIH Council of Public Representatives, or COPR.

"It has been my role in life to advocate for Native Americans and to get more Native Americans to be part of the research process—not as subjects, but as new researchers," Mala explains. "I felt that, by serving on COPR, I could raise awareness of Native American needs and health disparities of all minorities, which I believe are one of the major health problems in this nation."

Mala is on his way to South Dakota to participate in listening circles with National Library of Medicine Director Donald A. B. Lindberg, M.D. "We're bringing tribes of North and South Dakota together to talk about their needs," Mala says. "We'll say, 'Tell us what you need and let us see if we can respond.' It's the way I think government should be."

He also wants to help the NIH translate its research findings into terms that the public can understand. "The public wants to see results they can relate to," Mala says. "I think it's good



government and good practice to take all these very complicated genome concepts and break them down so the man on the street can understand and appreciate them. The NIH will get more support, and people affected with diseases will have a lot of new hope that wasn't there before. The public wants a sense of hope."

Mala says he encourages everyone to get involved with the NIH. "Anyone can apply to be a COPR member. It's not just well-connected people," he continues. "All of us as citizens of the United States own the NIH. This is our research arm. We should all be part of it, contributing our time, or at least investing the time to know what's going on."

(DCLG). DCLG ensures that those who experience the burden of cancer also help shape NCI's efforts to eradicate the disease. In 2001, NCI added the Consumer Advocates in Research and Related Activities (CARRA), who work alongside NCI staff and research advisors in peer review panels, site visits, and other projects.

TRAINING THE NEXT GENERATION

In the 1940s, training future generations of laboratory and clinical researchers became an important goal of federal funding of science. The NIH supports training that enables young scientists to become skilled investigators who are able to apply their talents to future medical challenges. Trainees at the precollege, predoctoral, or postdoctoral level are usually given stipends to train at the NIH or at medical schools and universities around the country. The NIH has most recently focused on improving prospects for under-represented minorities and individuals with disabilities, and on improving the quality of training programs. Here is a small sampling of the extensive

offerings made available with NIH support (see also *http://grants1.nih.gov/training/*).

■ When an important area of research has too few researchers, the NIH takes action. For example, the first priority for the NIH Stem Cell Task Force, according to James F. Battey, Jr., M.D., Ph.D., chairman of the task force, is to increase the number of researchers trained to work with human embryonic stem cells. "There are probably no more than 30 to 40 principal investigators," says Battey, who is also director of the National Institute on Deafness and Other Communication Disorders. "I could see the field growing five- to 10-fold over the next five years." To make it happen, the NIH is offering training funds to established investigators, short-term training courses for novices, and funds called administrative supplements for scientists to add embryonic stem cells to their research portfolios.

High school students studying science visit NIH labs to boost their interest in research careers.

■ The NIH Academy is a training program designed to enhance research dedicated to the elimination of health disparities in the United States through development of a diverse cadre of biomedical science researchers. In fiscal year 2002, 10 women and five men came to the NIH campus for a year of research training before attending medical or graduate school.

■ The NIH Undergraduate Scholarship Program offers competitive college scholarships to exceptional students from disadvantaged backgrounds who are committed to biomedical, behavioral, or social science research careers at the NIH. The program includes a mentored, residential research experience at the NIH and requires a year of service to the NIH as payback for each year of scholarship.

■ The NIH offers two one-year programs for medical students who want to learn more about research. One, co-sponsored with the Howard Hughes Medical Institute, brings medical students into research laboratories on the NIH campus. The second, the Clinical Research Training Program, supported by a grant from Pfizer, Inc., offers medical students a chance to learn how to conduct clinical research, from writing protocols to protecting human subjects to enrolling patients.

■ The NIH has more than 1,700 Visiting Fellows from around the world who participate in medical research on campus.

■ The NIH repays up to $35,000 per year of educational debt for health professionals who are pursuing careers in clinical, pediatric, contraception and infertility, or health disparities research; for clinical researchers from disadvantaged backgrounds; and intramural researchers doing AIDS research (see *http://lrp.info.nih.gov*).

■ SPINES (Summer Program in Neuroscience, Ethics, and Survival) is a unique program sponsored by the National Institute of Mental Health targeted to minorities underrepresented in neuroscience. The program is held every summer at the Marine Biological Laboratory in Woods Hole, Massachusetts. It provides a rich, one-month research experience in neuroscience, as well as training in the responsible conduct of research, grant writing, teaching, and public speaking. Students have the option of doing an extra month of research in the laboratory of a SPINES mentor.

■ Minority students, individuals with disabilities, and women have been encouraged and supported to choose careers in medical research through the National Institute of Neurological Disorders and Stroke (NINDS) Summer Program in Neurological Sciences. During its 18-year history, the program has trained more than 3,000 students, who spend a summer in NINDS laboratories on the Bethesda campus, receiving hands-on research experience and mentoring.

SHARING THE WEALTH

To facilitate medical research around the world, the NIH makes available resources such as tissue, reagents, and engineered cells. Links to many of these resources are available at *www.nih.gov/science*.

- The National Cancer Institute provides normal, benign, precancerous, and cancerous human tissue to the scientific community for basic and developmental studies.

- The AIDS Reagent Program is a unique worldwide resource of state-of-the art reagents for HIV and AIDS research. It has more than 4,300 reagents (cell lines, proteins, antibodies, viruses). More than 139,000 vials have been shipped to scientists from the United States and 63 foreign countries.

- The NIH has created a Human Embryonic Stem Cell Registry that lists the human embryonic stem cell lines—at varying stages of development—that meet the eligibility criteria for federal funding set forth by President George W. Bush in 2001. Contact information and details on how to apply for grants to study these cell lines are online at *http://stemcells.nih.gov/index.asp*.

- GenBank is the NIH database of all publicly available DNA sequences. It contains the sequence for the human genome, as well as genomes of the mouse and more than 1,000 organisms. GenBank is accessed on the Web more than 300,000 times daily by some 50,000 researchers (see *www.ncbi.nlm.nih.gov/Genbank*).

- The National Center for Research Resources supports the American Type Culture Collection, where scientists can obtain everything from bacterial strains that came from Louis Pasteur's laboratory to the DNA segments of practically every expressed gene in mice and humans. Researchers order about 235,000 items annually, including microbes, cell lines from more than 150 species, and recombinant DNA materials.

NIH PROFILE

FRANCIS COLLINS

The NIH, through the National Human Genome Research Institute (NHGRI), directed by Francis S. Collins, M.D., Ph.D., was the driving force behind the international collaboration that completed the high-quality sequencing of the human genome. That massive accomplishment—sequencing the three billion DNA letters of our genome—has touched off a revolution in biological research. When the Human Genome Project was launched in 1990, many in the scientific community were deeply skeptical about whether its audacious goals could be achieved. But they were, ahead of schedule and under budget. The international network of researchers—hundreds of scientists at 20 sequencing centers in China, France, Germany, Great Britain, Japan, and the United States—has produced an amazing array of advances that weren't expected until much later. PricewaterhouseCooper's Endowment for the Business of Government described the Human Genome Project as a model of a well-managed large government project. Its report explained, "Partnerships across agencies, sectors, and nations are likely to be the wave of the future for large-scale public efforts at the frontier of knowledge."

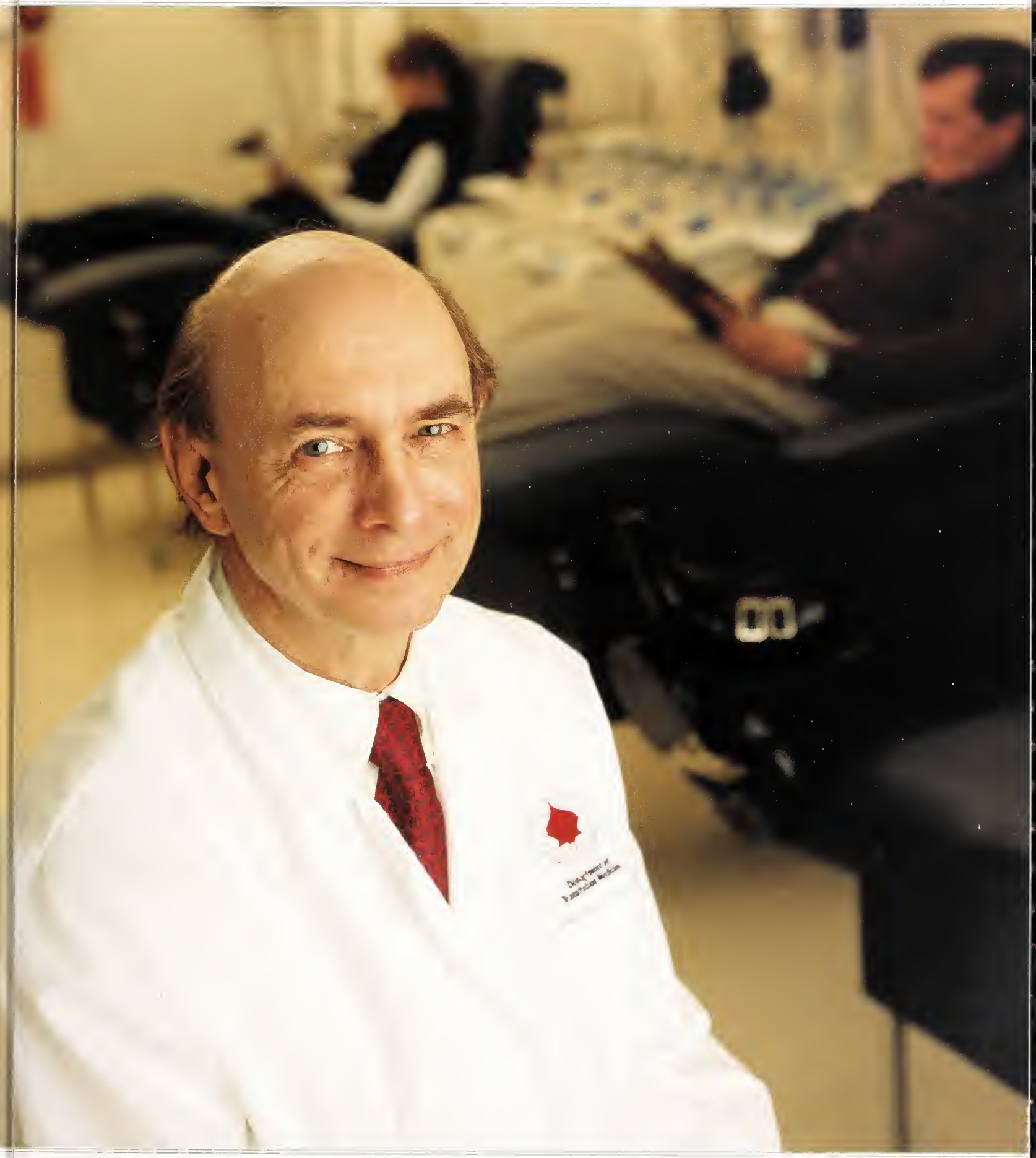
Collins and his NHGRI colleagues, Eric D. Green, M.D., Ph.D., Alan E. Guttmacher, M.D., and Mark S. Guyer, Ph.D., have already presented an ambitious plan for the next phase of genomics research. With the help of hundreds of scientists and members of the public, they've laid out *A Vision for the Future of Genomics Research,* which sets forth a series of "grand challenges" intended to energize the scientific community to use the newfound description of the genome to uncover the causes of disease and to develop bold new approaches to the prevention and treatment of disease. The plan's far-reaching goals cover resources; technology development; computational biology; training; ethical, legal, and social implications; and education. As with the Human Genome Project itself, early, open access to results will be a priority. The full plan is available at *www.genome.gov/11007524*.

The Nation's Research Hospital

In 2003, the Warren Grant Magnuson Clinical Center at the National Institutes of Health marked 50 years of patient care and progress. More than a quarter of a million patients from around the country have been seen since the doors opened in July 1953.

Major milestones in medical treatment have taken place at the Clinical Center: The first cures for childhood leukemia using multi-agent chemotherapy; the first successful replacement of the heart's mitral valve; hydroxyurea as the first drug to treat sickle cell anemia; AZT as the first treatment for AIDS. The list goes on and on.

➤ The U.S. blood supply is much safer because of decades-long work by Harvey Alter and his scientist colleagues at the NIH Clinical Center. See page 68.



The Clinical Center has served as an international model for conducting clinical research. It is the focal point on the NIH campus for research with patients and for training clinical scientists. The 14-story research hospital contains 267 beds, 15 outpatient clinics, and more than 1,600 laboratories. A replacement for the hospital and some of the laboratories, the Mark O. Hatfield Clinical Research Center, is set to open in December 2004, with 240 beds and 90 day-hospital stations.

The Clinical Center takes on studies that would be difficult to do anywhere else. About half of its protocols are clinical trials of new drugs, mostly phase I or II trials—when an agent is tested in humans for the first time to determine safety and efficacy. If these early studies show promise, the drugs move into phase III trials, which are usually conducted by extramural researchers in large groups of patients.

The other half of the protocols are natural histories of diseases—often rare diseases—to reveal how they affect the patients and to develop new medical interventions or approaches to care. The natural history studies are typically long term and usually involve patients from across the nation and around the world. Many of these studies probably would never have been conducted if they had not been done in the Clinical Center.

MINING THE BLOOD

Among all of the path-blazing research going on at the Clinical Center, some of the Department of Transfusion Medicine's work stands out.

The Mark O. Hatfield Clinical Research Center will open on the NIH campus in late 2004, becoming home to new inpatient units, day hospitals, and research labs.

An Answer to Blood Shortages. People with hereditary hemochromatosis, an inherited disorder that overloads their body organs with iron, may become super blood donors. Standard treatment for these individuals is regular removal of quantities of blood, which in most medical centers is discarded. Yet people with hemochromatosis are generally healthy and many meet blood donor eligibility criteria. Red blood cells from hemochromatosis donors have normal amounts of iron and cannot transmit the iron-overload tendency. The Clinical Center's Department of Transfusion Medicine has developed a model system—safe for both donor and recipient—that uses the blood of these individuals

Since 1990, the Children's Inn at the NIH has been a refuge for seriously ill children and their families while the children receive treatment at the Clinical Center. The Inn is a private, non-profit residence that is a home away from home for more than 1,000 children and their families each year. With generous donations, the largest from Merck & Co., Inc., a new two-level wing opened in 2004 to provide space for more families.

One of the Tough Cases

When Dan Magrino entered the NIH Clinical Center for the first time on December 8, 2002—worn out and anxious in search of treatment for Cushing's syndrome—he didn't have high hopes for what he called a "government institution." He left with a different perspective. "There is no place like it," he says. "This is the best of America. I'm proud of this place, proud to see my tax dollars at work this way."

Months before, the 37-year-old resident of West Paterson, New Jersey, had added a basketball-sized potbelly to his 5-foot 10-inch, athletic frame. He kept putting on the pounds, no matter how much he dieted and exercised. His clothes didn't fit, his blood pressure was high, and he had a short temper—just ask his wife, Sharon. His primary care doctor blamed the weight gain on junk food and beer, but Magrino was not a beer drinker, and he exercised and ate right. When his blood pressure remained high, his doctor ran tests that pointed to too many possibilities: prostate cancer, diabetes, kidney problems, even liver disease.

After visits with several specialists and more tests, he had a diagnosis: Cushing's syndrome, a rare condition that occurs mostly in children and older women. But the cause of his ailment was harder to pinpoint. Cushing's is a complicated disorder involving the adrenal gland, which secretes cortisol, one of the "fight or flight" hormones that enable us to respond to threats and stresses. In Cushing's syndrome, the body produces too much cortisol. The abundance of cortisol causes weight gain, hypertension, joint aches and pains, muscle weakness, irritability, and difficulty concentrating. But to be treated effectively, its cause needs to be determined, and there are several possibilities: taking high doses of steroids, a tumor in the pituitary gland, an abnormality in the adrenal glands, or an "ectopic" tumor that stimulates the adrenal glands to produce cortisol. Because ectopic tumors can grow anywhere, finding one can involve a search of the entire body.

A CT (computed tomography) scan of his abdominal region led to surgery. Doctors removed his right adrenal gland, figuring that would do the trick. It didn't. Magrino's body told him he still had Cushing's, his cortisol level was as high as ever, and he was getting fed up.

When Magrino's endocrinologist suggested he go to the NIH but didn't get him in, the former merchant marine took matters into his own hands. The worst the NIH could tell him was no, he reasoned. He had the name of the Cushing's doctor, and he found a toll-free number for the NIH on the Internet.

The employee who answered the phone found two Cushing's protocols, or studies, at the NIH and took Magrino's information. Magrino asked, "Are both protocols run by Dr. Lynnette Nieman?"

"Yes," she replied. "Would you like to speak to her?" He did. Magrino recalls, "This wonderful, wonderful woman came on the line. No pompous attitude, no prima donna syndrome." Nieman, who has seen nearly a thousand Cushing's patients—as many as anyone in the world—was part of the NIH team that had developed the tests that Magrino would undergo, tests that were far more accurate than those he'd already had. The tests detected a tiny tumor in his pituitary gland—one that an earlier MRI had missed.

Ed Oldfield, M.D., chief of surgical neurology at the National Institute of Neurological Disorders and Stroke, removed the affected area of Magrino's pituitary. Nieman can't guarantee that he's cured—about 12 percent of patients have a recurrence. Magrino's joints still ache, and his adrenal gland and pituitary glands may take up to 18 months to start working again. But he has lost 35 pounds, and once the excess cortisol was out of his system, he began feeling and behaving more like himself again.

He says he's proud of himself for being persistent about getting to the root of his problem and taking the initiative to find out what the NIH Clinical Center could do for him.

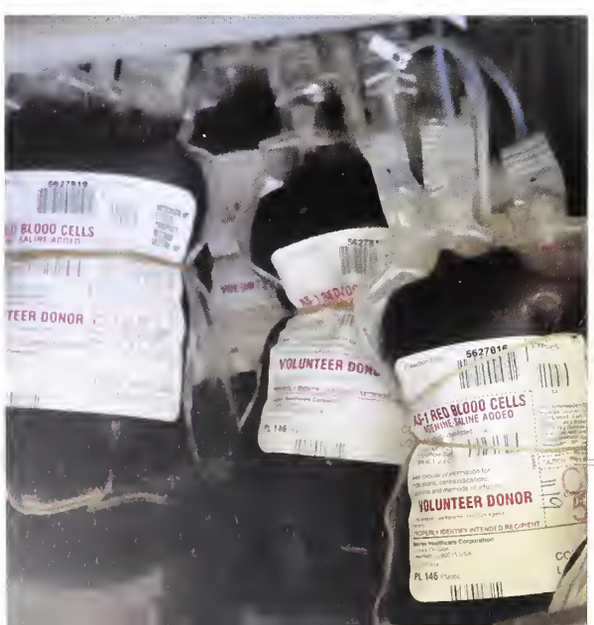
for transfusion. The first 150 research subjects entered in the system now supply about 1,000 units of red blood cells per year, or 18 percent of the red blood cells used for transfusion in the Clinical Center. Applying such a system nationwide should help address blood shortages in the United States.

Islet Cells for Diabetes. The Clinical Center is one of 10 centers that are isolating pancreatic islet cells from cadaver organ donors to be used for transplants into the livers of patients with type 1 diabetes. This approach may free patients from dependence on daily insulin (see page 36).

Improving Platelet Transfusion Success. More than 30,000 units of platelets are collected each year for transfusion at the Clinical Center. About 10 percent of patients will not have a good response to platelet transfusions. Clinical Center scientists found, 35 years ago, that antibodies to human leukocyte antigens (HLA) are responsible for rejection of the transfused platelets. A molecular analysis study is under way to determine if closer donor/recipient matching, using newer DNA typing techniques, can improve transfusion success.

Ending Transfusion-transmitted Infections. Blood donors and recipients are being studied to determine the frequency and importance of transfusion-transmitted infections. Specimens from donated blood are tested for infectious agents and stored long term. Transfusion recipients will be followed for at least six months to determine if they have developed infections from transfusions and what impact this might have on their health. This long-term blood storage program has helped eradicate post-transfusion infections with hepatitis B and C and HIV.

Clinical Center scientists have developed a safe way to address blood shortages in the United States.



NIH PROFILE

MAKING THE BLOOD SUPPLY SAFER

Americans very rarely get hepatitis or AIDS from blood transfusions. And it's because of the work of NIH scientists.

In the 1960s, a newly minted doctor named Harvey Alter was trying to figure out why some patients developed high fevers after receiving blood transfusions. "My theory was that people might be reacting to plasma proteins that were different from their own." In the Clinical Center's Blood Bank, he had set up a method for testing the serum of repeatedly transfused patients against the serum of donors, which produced a specific line in a plate containing agar gel, reflecting the presence of antibodies. One day a colleague told Alter that Baruch S. Blumberg, M.D., Ph.D., a geneticist working in another building at the NIH, was doing similar work.

"The beauty of the NIH is that I went to talk to him the very next day, and by that evening we had established a collaboration," says Alter, 68. Their work together led to the discovery in 1964 of the Australia antigen, which Blumberg later showed to be the surface coating of the hepatitis B virus, which led to the isolation of this medically important virus.

At the same time, the Blood Bank was concerned that the high volume of blood needed during open-heart bypass surgery might lead to a high rate of transfusion-transmitted infection, especially hepatitis. Alter took specimens from each of the donors for open-heart surgery. He also took samples from the surgery patients, before and for months to years after surgery—the frequency of the sampling depending on whether or not he found any evidence of transfusion-transmitted hepatitis. A whopping one third of those patients had received blood containing hepatitis B, which eventually inflamed their livers, producing hepatitis.

Alter froze and stored those donor and patient specimens, which required an enormous serum repository. "This all evolved at a time when such a repository was quite expensive and simply wasn't done, and this turned out to be a gold mine,"

says Harvey Klein, M.D., who became department director in 1984, the year the Blood Bank was renamed Transfusion Medicine.

Studies done in 1970 had shown that patients who received at least one unit of blood from a paid donor had about a 50 percent chance of developing hepatitis. Those who received only volunteer blood had a 7 percent chance—a dramatic difference. The Blood Bank had been buying about half its blood from commercial blood establishments in Baltimore and Memphis, where donors often sold their blood to buy alcohol or drugs. So in 1970, the Blood Bank switched to an all-volunteer system, at the same time adding a test for hepatitis B surface antigen. Those two measures alone reduced the hepatitis rate from 30 percent before 1970 to about 11 percent after. "In truth," says Alter, "nothing we've ever done since that time has had that dramatic an impact, because there were so many cases to prevent." When they added more sensitive tests, hepatitis B virtually disappeared as a problem in the Blood Bank. These policies soon became national standards.

In collaboration with Bob Purcell, M.D., and Stephen Feinstone, M.D., National Institute of Allergy and Infectious Diseases, Alter determined that whatever was triggering the rest of the transfusion-associated hepatitis was neither hepatitis A nor hepatitis B. From 1975 to 1989, they called the unknown agent(s) "non-A, non-B hepatitis" (NANBH), showed that it produced hepatitis in chimpanzees, and searched for a simple blood test to distinguish those who carried the infection from those who did not. So many laboratories claimed to have produced tests for NANBH that from his warehouse of frozen samples, Alter developed a coded panel of specimens, some of which were known to be from non-A, non-B cases and some of which were from control subjects. Roughly 20 labs asked to have their tests applied to the panel. None produced a successful test until 1989, when a commercial firm named Chiron, which had secretly been working to clone the NANBH agent since 1983, asked Alter to run its test against his panel. Chiron's test worked.

The beauty of having a repository of well-followed, highly pedigreed patient specimens, says Alter, was that they could truly show they had found the marker for what was now renamed the "hepatitis C virus." They published a paper in the *New England Journal of Medicine* ("the fastest paper I ever wrote"), and by 1990 a test was in place in every U.S. blood bank. "This kind of long-term, non-directed research could really only have been done here at the Clinical Center," says Alter. "If I had gone to a granting authority in 1970 and said, 'I don't know what hepatitis agents are, but I think there are some out there and I want to find them, and I want to follow patients long term, because the natural history of hepatitis C or non-A, non-B, is 20, 30, 40 years—it's a very slowly evolving infection—so I'd like to be funded for about 30 years and really study this,' I couldn't do it! But here at the NIH, each year I would get some money to do something and just kept going."

In 1976, Baruch Blumberg received a Nobel Prize for his work on the Australia antigen and hepatitis B. In 2000, Harvey Alter and Chiron's Michael Houghton, Ph.D., shared a Lasker Award for their work. Alter has been widely recognized for reducing the risk of blood transfusion-associated hepatitis from 30

percent in 1970 to virtually zero in the year 2000. The risk of contracting hepatitis C from a pint of blood is now about 1 in two million.

When, in the early 1980s, a new disease came along, an acquired disease of severe immunodeficiency, there was a suspicion that it might be transmitted by blood, but no one knew for sure. The work done in the Blood Bank—and that repository of frozen blood specimens—became important both for AIDS generally and for the safety of the nation's blood supply.

Excerpted from "Building Ten at Fifty. Fifty Years of Clinical Research at the NIH Clinical Center," written for the NIH by Pat McNees.

Payoff from Patient Studies

What are we learning from clinical studies? Studies with patients and healthy volunteers have yielded findings that, when communicated to doctors and the public, will result in more lives saved and healthier lives. Here are some recent advances:

Lifestyle change can prevent type 2 diabetes—in a big way.

Intensive counseling on effective diet, exercise, and behavior change reduced risk for developing diabetes by 58 percent. The intervention worked particularly well for study participants ages 60 and older, whose risk dropped by 71 percent. The drug metformin was also effective, though less so, at reducing diabetes risk.

High-speed MRI detects more heart attacks, faster.

Magnetic resonance imaging (MRI) can detect heart attacks in patients who go to the emergency room with chest pain faster and more accurately than traditional methods. This result may usher in a dramatic change in how heart attacks are diagnosed, and how rapidly patients receive treatment once they arrive at the hospital—a key factor in treatment success. In a collaboration involving the National Heart, Lung, and Blood Institute (NHLBI), the NIH Clinical Center, and Suburban Hospital in Bethesda, Maryland, MRI did a better job of detecting heart attacks and unstable angina than three standard tests. Andrew Arai, M.D., NHLBI's principal investigator of the study, says, "MRI allows us to look at how well the heart is pumping, how good the supply of blood to the heart is in specific areas, and whether there is evidence of permanent damage to the heart."

Exercising regularly, reducing fat and calorie intake, and losing weight can reduce risk for type 2 diabetes.

Eight-year-old twins, Kyle and Ian Brown, both have autism.

ACE inhibitors slow kidney disease in African Americans.

The largest clinical trial ever conducted in African Americans with kidney disease has concluded that an angiotensin-converting enzyme (ACE) inhibitor is superior to two other classes of drugs for slowing kidney disease caused by hypertension. "The results of this trial will significantly improve the health of thousands of African Americans who suffer from kidney disease due to hypertension," says John Ruffin, Ph.D, director of the National Center on Minority Health and Health Disparities, which funded the study with the National Institute of Diabetes and Digestive and Kidney Diseases. "It also demonstrates the benefit of focusing research on populations most affected."

Anti-psychotic drug helps children with autism.

The drug risperidone, one of a newer class of anti-psychotic medications, was successful and well tolerated for treating serious behavioral disturbances such as self-injury, aggression, and tantrums in children with autism. This large, multisite clinical trial, funded by the National Institute of

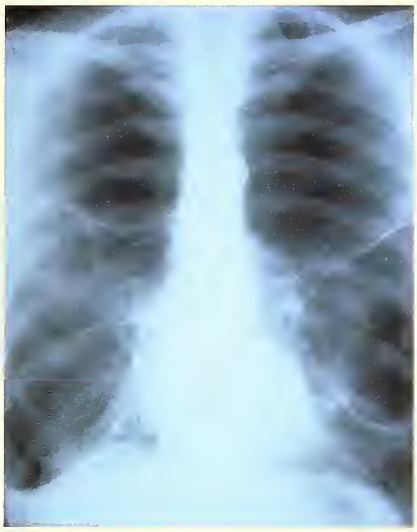
Mental Health and the National Center for Research Resources, showed the largest positive effect by a medication ever observed in children with autism.

First prostate cancer prevention drug found, but not all men benefit.

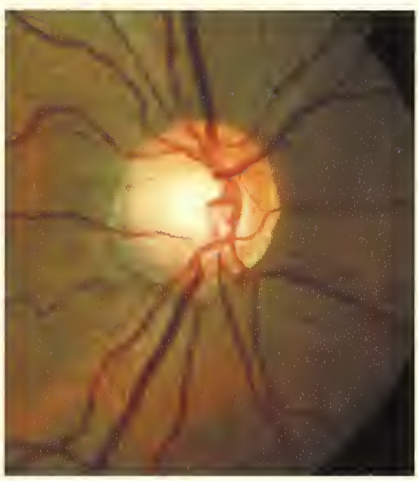
The Prostate Cancer Prevention Trial, involving nearly 19,000 men, showed that a man's risk for developing prostate cancer could be reduced by daily use of finasteride, a drug that affects male hormone levels and is used to treat benign prostate growth. One cautionary note is under investigation: men who did develop prostate cancer while taking finasteride were more likely to have a high-grade or aggressive cancer.

Treatment decisions for emphysema more clear-cut.

Uncertainty about the risk of lung volume reduction surgery, its benefits, and the best criteria for selecting patients led the NHLBI and the Center for Medicare and Medicaid Services to sponsor a five-year, multicenter, randomized clinical study, the National Emphysema Treatment Trial. Results show that, on average, patients with severe emphysema who undergo removal of diseased portions of the lungs are more likely to function better after two years and do not face an increased risk of death compared with those who receive standard medical therapy. Importantly, the trial pointed out two key patient characteristics that predict the outcome of surgery. With these results in hand, the U.S. Medicare program quickly responded by stating that it will pay for the surgery for beneficiaries who meet the criteria for a good outcome. Nearly two million people in the United States suffer from emphysema.



Emphysema bubbles in the left lung severely impede breathing capacity.



A view of the eyeball's interior shows glaucoma's damage to the optic nerve.

Lowering eye pressure can slow glaucoma.

Results from a study sponsored by the National Eye Institute showed that eye drops used to treat elevated pressure inside the eye can delay the onset of glaucoma, a leading cause of blindness in the United States. A second study showed that immediate treatment of patients who have the early stage of the most common form of glaucoma can slow progression of the disease.

Gene tied to doubled risk of depression after life stresses.

People with the "short" version of a mood-related gene who have suffered multiple stressful events are twice as likely to develop depression as people with the "long" version of the gene, according to research funded in part by the National Institute of Mental Health. No matter how many stressful life events they endured, people with the protective version of the serotonin transporter gene experienced no more depression than people who were totally spared stressful life events. The stressful events included problems with employment, finances, housing, health, and relationship woes or a history of child abuse.

Components of the NIH

Through 27 institutes and centers, each with its own broadly defined mission, the NIH provides leadership and financial support to researchers in every state and throughout the world.

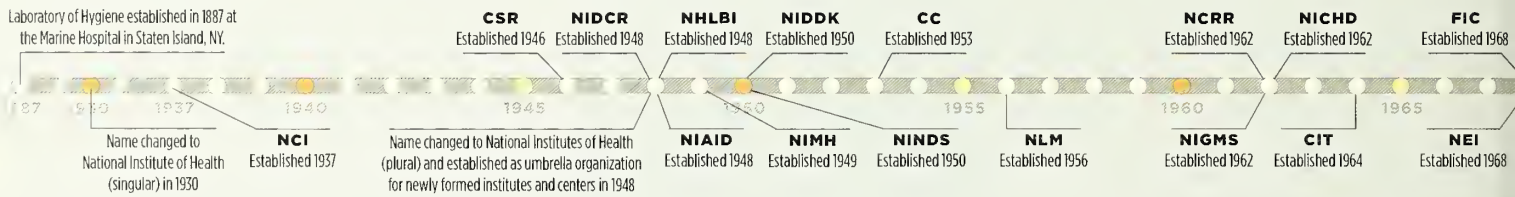
OFFICE OF THE DIRECTOR (OD)
The Office of the Director is the central office at the NIH for its 27 institutes and centers. OD is responsible for setting policy for the NIH and for planning, managing, and coordinating the programs and activities of all the NIH components. OD's program offices include the Office of AIDS Research, the Office of Research on Women's Health, and the Office of Technology Transfer, among others.

NATIONAL CANCER INSTITUTE (NCI)
Established 1937
NCI leads a national effort to eliminate the suffering and death caused by cancer. Through basic and clinical medical research and training, NCI conducts and supports research that will lead to a future in which cancer can be prevented before it starts, cancers that do develop are identified at the earliest stage, cancers are eliminated through innovative treatment interventions, and those cancers that cannot be eliminated are biologically controlled so they become manageable, chronic diseases.

NATIONAL EYE INSTITUTE (NEI)
Established 1968
NEI conducts and supports research that helps prevent and treat eye diseases and other disorders of vision. This research leads to sight-saving treatments, reduces visual impairment and blindness, and improves the quality of life for people of all ages. NEI-supported research has advanced knowledge of how the eye functions in health and disease.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)
Established 1948
NHLBI provides leadership for a national program in diseases of the heart, blood vessels, lungs, and blood; blood resources; and sleep disorders. Since October 1997, NHLBI has also had administrative responsibility for the NIH Woman's Health Initiative. The institute plans, conducts, fosters, and supports an integrated and coordinated program of basic research, clinical investigations and trials, observational studies, and demonstration and education projects.

NATIONAL HUMAN GENOME RESEARCH INSTITUTE (NHGRI)
Established 1997
NHGRI led the NIH contribution to the Human Genome Project, a worldwide research effort that, in April 2003, successfully completed its goal of sequencing the three billion base pairs in the human genetic blueprint. NHGRI's mission has expanded to encompass a broad range of studies aimed at elucidating the structure and function of the human genome, as well as exploring its role in health and disease. NHGRI's intramural research program develops and implements technology for understanding, diagnosing, treating, and preventing genetic diseases.



NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES (NIAMS)
Established 1986
NIAMS supports research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases, the training of basic and clinical scientists to carry out this research, and the dissemination of information on research progress in these diseases.

NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING (NIBIB)
Established 2000
NIBIB improves health by promoting fundamental discoveries, design and development, and translation and assessment of technological capabilities in biomedical imaging and bioengineering, enabled by relevant areas of information science, physics, chemistry, mathematics, materials science, and computer sciences.

NATIONAL INSTITUTE ON AGING (NIA)
Established 1974
NIA leads a national program of research on the biomedical, social, and behavioral aspects of the aging process; the prevention of age-related diseases and disabilities; and the promotion of a better quality of life for all older Americans.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)
Established 1970
NIAAA conducts research focused on improving the treatment and prevention of alcoholism and alcohol-related problems to reduce the enormous health, social, and economic consequences of this disease.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)
Established 1948
NIAID supports basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses, including HIV/AIDS and other sexually transmitted diseases, illness from potential agents of bioterrorism, tuberculosis, malaria, autoimmune disorders, asthma, and allergies.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD)
Established 1962
NICHD research on fertility, pregnancy, growth, development, and medical rehabilitation strives to ensure that every child is born healthy and wanted and grows up free from disease and disability.

NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS (NIDCD)
Established 1988
NIDCD conducts and supports biomedical research and research training on normal mechanisms as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language that affect 46 million Americans.

NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH (NIDCR)
Established 1948
NIDCR provides leadership for a national research program designed to understand, treat, and ultimately prevent the infectious and inherited craniofacial, oral, and dental diseases and disorders that compromise millions of human lives.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES (NIDDK)
Established 1950
NIDDK conducts and supports basic and applied research and provides leadership for a national program in diabetes, endocrinology, and

metabolic diseases; digestive diseases, nutrition, overweight, and obesity; and kidney, urologic, and hematologic diseases. Several of these diseases are among the leading causes of disability and death; all seriously affect the quality of life of those who have them.

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)
Established 1973
NIDA leads the nation in bringing the power of science to bear on drug abuse and addiction through support and conduct of research across a broad range of disciplines and rapid and effective dissemination of results of that research to improve drug abuse and addiction prevention, treatment, and policy.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS)
Established 1969
NIEHS reduces the burden of human illness and dysfunction from environmental causes by defining how environmental exposures, genetic susceptibility, and age interact to affect an individual's health.

all over the world. To accomplish this goal, NINDS supports and conducts research, both basic and clinical, on the normal and diseased nervous system, fosters the training of investigators in the basic and clinical neurosciences, and seeks better understanding, diagnosis, treatment, and prevention of neurological disorders.

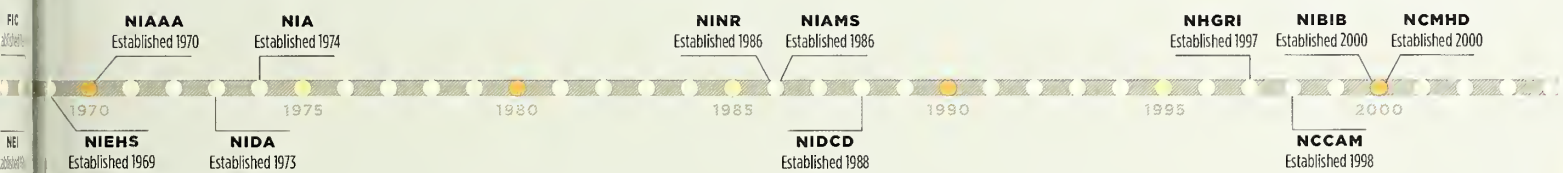
NATIONAL INSTITUTE OF NURSING RESEARCH (NINR)
Established 1986
NINR supports clinical and basic research to establish a scientific basis for the care of individuals across the lifespan—from the management of patients during illness and recovery to the reduction of risks for disease and disability; the promotion of healthy lifestyles; the promotion of quality of life in those with chronic illness; and the care for individuals at the end of life. This research may include families within a community context, and it also focuses on the special needs of at-risk and underserved populations, with an emphasis on health disparities.

and refers these applications to their respective funding components. CSR seeks to develop innovative and flexible ways to review NIH applications for scientific and technical merit so the NIH can fund the most promising researchers.

JOHN E. FOGARTY INTERNATIONAL CENTER (FIC)
Established 1968
FIC promotes and supports scientific research and training internationally to reduce disparities in global health.

NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE (NCCAM)
Established 1998
NCCAM is dedicated to exploring complementary and alternative medicine (CAM) practices in the context of rigorous science, training CAM researchers, and disseminating authoritative information.

NATIONAL CENTER ON MINORITY HEALTH AND HEALTH DISPARITIES (NCMHD)
Established 2000
The mission of NCMHD is to promote minority



NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES (NIGMS)
Established 1962
NIGMS supports basic biomedical research that is not targeted to specific diseases. NIGMS funds studies on genes, proteins, and cells, as well as on fundamental processes like communication within and between cells, how our bodies use energy, and how we respond to medicines. The results of this research increase understanding of life and lay the foundation for advances in disease diagnosis, treatment, and prevention. NIGMS also supports research training programs that produce the next generation of biomedical scientists, and it has special programs to encourage under-represented minorities to pursue biomedical research careers.

NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH)
Established 1949
NIMH provides national leadership dedicated to understanding, treating, and preventing mental illnesses through basic research on the brain and behavior and through clinical, epidemiological, and services research.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS)
Established 1950
The mission of NINDS is to reduce the burden of neurological diseases—*a* burden borne by every age group, every segment of society, and people

NATIONAL LIBRARY OF MEDICINE (NLM)
Established 1956
NLM collects, organizes, and makes available biomedical science information to investigators, educators, and practitioners and carries out programs designed to strengthen medical library services in the United States. Its electronic databases, including MEDLINE and MEDLINEPlus, are used extensively throughout the world by both health professionals and the public.

CENTER FOR INFORMATION TECHNOLOGY (CIT)
Established 1964
CIT incorporates the power of modern computers into the biomedical programs and administrative procedures of the NIH by focusing on three primary activities: conducting computational biosciences research, developing computer systems, and providing computer facilities.

CENTER FOR SCIENTIFIC REVIEW (CSR)
Established 1946
CSR is the focal point at the NIH for the conduct of initial peer review, the foundation of the NIH grant and award process. The center organizes the groups of independent scientists who evaluate the majority of research and training grant applications sent to the NIH. In addition, the center receives all grant applications for the NIH, as well as for some other components of the U.S. Department of Health and Human Services,

health and to lead, coordinate, support, and assess the NIH effort to reduce and ultimately eliminate health disparities. In this effort, NCMHD conducts and supports basic, clinical, social, and behavioral research; promotes research infrastructure and training; fosters emerging programs; disseminates information; and reaches out to minority and other communities that experience health disparities.

NATIONAL CENTER FOR RESEARCH RESOURCES (NCRR)
Established 1962
NCRR advances biomedical research and improves human health through research projects and shared resources that create, develop, and provide a comprehensive range of human, animal, technological, and other resources. NCRR's support is concentrated in four areas: biomedical technology, clinical research, comparative medicine, and research infrastructure.

WARREN GRANT MAGNUSON CLINICAL CENTER (CC)
Established 1953
CC is the clinical research facility of the National Institutes of Health. As a national resource, it provides the patient care, services, and environment needed to initiate and support the highest-quality conduct of and training in clinical research.

NIH BY THE NUMBERS

The National Institutes of Health supports a thriving medical research enterprise. With the historic doubling of the NIH budget from 1998 to 2003, a record number of research grants are being awarded to scientists around the country, more young scientists are receiving training than ever before, and clinical trials—patient studies of new approaches to prevent, diagnose, and treat diseases—are receiving unprecedented support.

IN BRIEF

$27.8 billion
FY 2004 appropriations*#

75%
NIH share of annual federal spending on health R&D

84.8%
NIH budget invested in research outside NIH

$19.3 billion
FY 2004 dollars spent on research grants**

$8.5 billion
FY 2004 dollars spent on research training, R&D contracts, intramural research and other***

21,900
Scientists on extramural training grants, FY 2004

3,082
Institutions, worldwide, receiving NIH funds

212,000
Researchers, worldwide, supported by the NIH

6,000
Scientists on the NIH campus

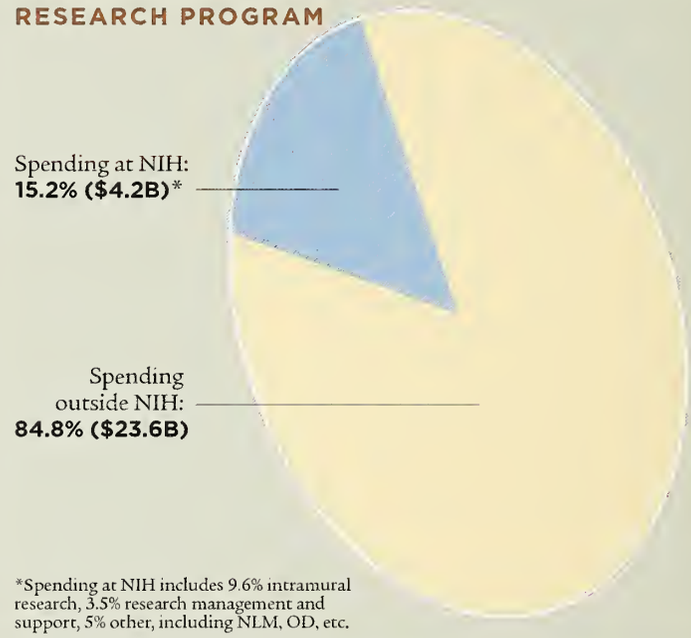
*Does not include Veterans Administration/Housing and Urban Development Superfund ($78 mil) or Office of National Drug Control Policy ($4 mil)

#FY 2004 budget figures are estimates. Actual obligations can not be determined until the close of FY 2004.

**Research grants include research projects, Small Business Innovation Research and Small Business Technology Transfers, research centers and other research.

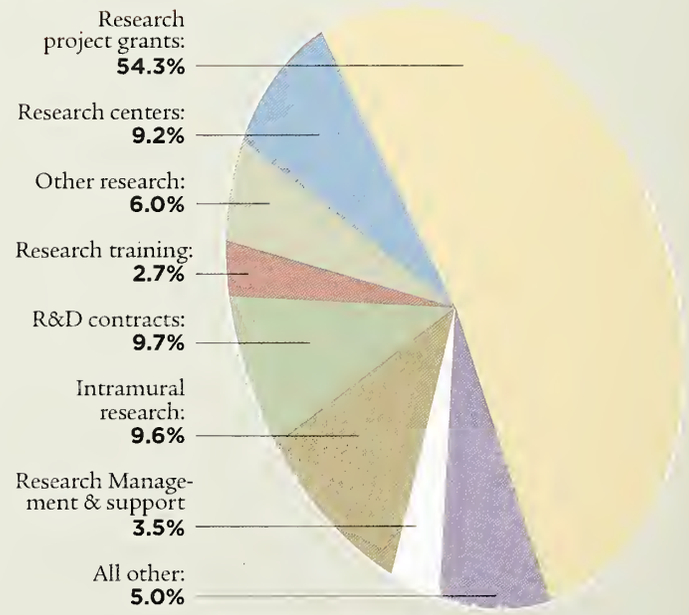
***Other = research management and support, cancer control, National Library of Medicine, extramural construction, Office of the Director, and buildings and facilities.

FUNDING AMERICA'S MEDICAL RESEARCH PROGRAM



*Spending at NIH includes 9.6% intramural research, 3.5% research management and support, 5% other, including NLM, OD, etc.

FY 2004 ESTIMATES BY MECHANISM



IMPACT OF THE DOUBLING OF THE BUDGET

The doubling of the NIH budget from 1998 to 2003 has already expanded our knowledge, enabling us to see farther than we could before. This increased investment enabled us to seize opportunities to move research forward and improve the health of Americans more rapidly than ever before. All of the institutes and centers have many new research projects under way.

NIH 10-YEAR TRENDS

	1994	1998	2003	% Change 98 – 03
Appropriations amount (in millions)	$10,938	$13,675	$27,067	98
NIH employees	16,235	15,159	17,574	16
Research grants funded	29,450	33,127	45,881	39
Research project grants funded*	24,050	27,073	36,187	34
Clinical trials dollars (in millions)	$1,130	$1,388	$2,723	96
Extramural scientists trained	16,790	17,880	27,371	53
Institutions receiving NIH funds	2,120	2,337	3,082	32

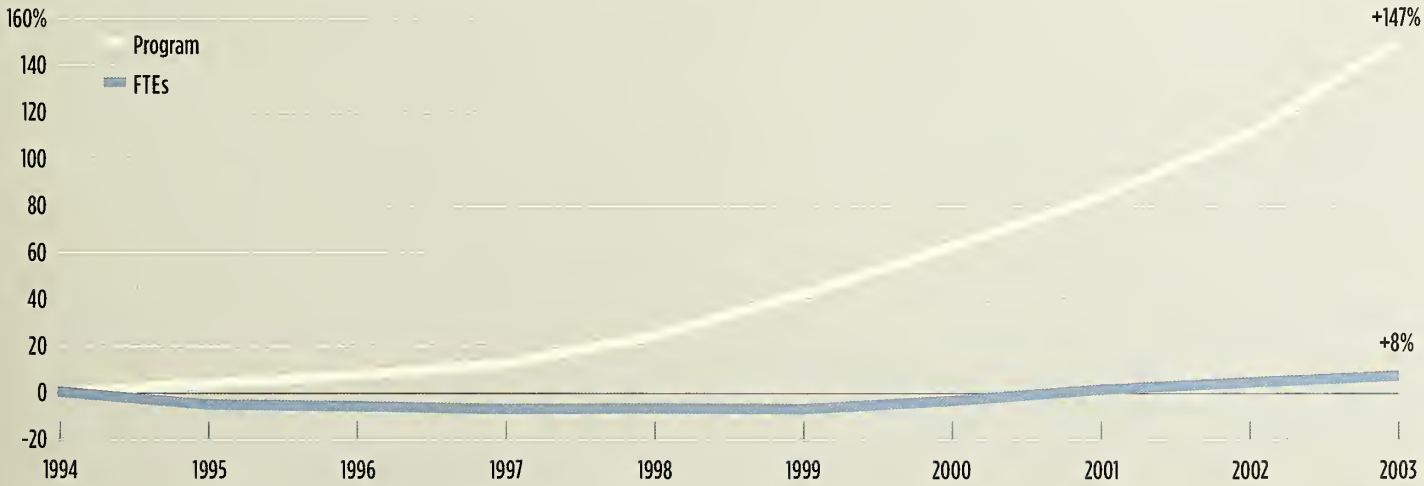
*Research project grants are awarded to institutions on behalf of a principal investigator to support medical research activities.

NUMBER OF GRANT APPLICATIONS AND SUCCESS RATES

The success rates shown below represent the likelihood that a competing research project grant application will be funded in a given fiscal year. Success rates vary among institutions and among types of grants. The data shown here represents NIH aggregate data.

% CHANGE IN FUNDING AND FTES FROM 1994 TO 2003

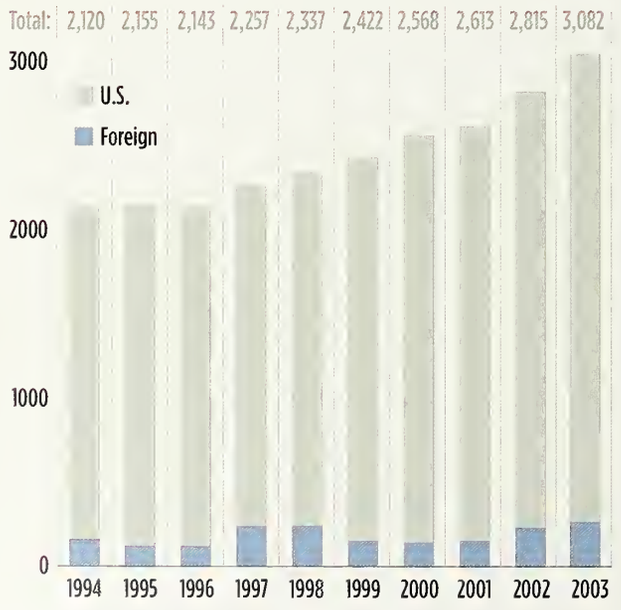
NIH funding has grown 147 percent over the past 10 years, while the number of full-time equivalents (FTEs), the number of people needed to manage this portfolio, has increased by only 8 percent. By aggressively using modern methods of management and information systems, we have prevented any substantial increase in FTEs and have reduced our research management and support expenses from 4.6 percent to 3 percent of the NIH budget.



FY 2004 APPROPRIATIONS FOR INSTITUTES AND CENTERS* (IN MILLIONS)

*CIT, CSR, and CC provide central services and are funded from appropriations to other components. B&F = buildings and facilities

NUMBER OF INSTITUTIONS RECEIVING NIH FUNDS




INSTITUTES OF HEALTH

The National Institutes of Health (NIH), a part of the U.S. Department of Health and Human Services, is the primary federal agency for conducting and supporting medical research. Helping to lead the way toward important medical discoveries that improve people's health and save lives, NIH scientists investigate ways to prevent disease as well as the causes, treatments, and even cures for common and rare diseases. Composed of 27 institutes and centers, the NIH provides leadership and financial support to researchers in every state and throughout the world.

Connecting to the NIH

For more information on the National Institutes of Health, go to the NIH Web site, www.nih.gov, to link to the latest reliable health information and news; more details about the National Institutes of Health and its 27 institutes and centers; and information about clinical trials.

Clinical Trials

If you are interested in participating in a clinical trial, go to *www.clinicaltrials.gov*

For information about clinical research being conducted at the NIH Clinical Center in Bethesda, MD, call 1-800-411-1222, TTY 866-411-1010.

NIH is an agency within the U.S. Department of Health and Human Services

National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892
(301) 496-4000

INSTITUTES

NCI National Cancer Institute
www.cancer.gov
1-800-4-CANCER (1-800-422-6237)

NEI National Eye Institute
www.nei.nih.gov
301-496-5248

NHLBI National Heart, Lung, and Blood Institute
www.nhlbi.nih.gov
301-592-8573
NHLBI Health Information Center 240-629-3255 (TTY)

NHGRI National Human Genome Research Institute
www.genome.gov
301-402-0911

NIA National Institute on Aging
www.nia.nih.gov
Aging information 1-800-222-2225
Alzheimers information 1-800-438-4380

NIAAA National Institute on Alcohol Abuse and Alcoholism
www.niaaa.nih.gov
301-443-3860

NIAID National Institute of Allergy and Infectious Diseases
www.niaid.nih.gov
301-496-5717

NIAMS National Institute of Arthritis and Musculoskeletal and Skin Diseases
www.niams.nih.gov
1-877-22NIAMS

NIBIB National Institute of Biological Imaging and Bioengineering
www.nibib.nih.gov
301-451-6772

NICHD National Institute of Child Health and Human Development
www.nichd.nih.gov
1-800-370-2943

NIDCD National Institute on Deafness and Other Communication Disorders
www.nidcd.nih.gov
1-800-241-1044 (voice)
1-800-241-1055 (TTY)

NIDCR National Institute of Dental and Craniofacial Research
www.nidcr.nih.gov
301-496-4261

NIDDK National Institute of Diabetes and Digestive and Kidney Diseases
www.niddk.nih.gov
Diabetes 1-800-860-8747
Digestive disorders 1-800-891-5389
Overweight and obesity 1-877-946-4627
Kidney and urologic diseases 1-800-891-5390
Other 301-496-3583

NIDA National Institute on Drug Abuse
www.nida.nih.gov
301-443-1124

NIEHS National Institute of Environmental Health Sciences
www.niehs.nih.gov
919-541-3345

NIGMS National Institute of General Medical Sciences
www.nigms.nih.gov
301-496-7301

NIMH National Institute of Mental Health
www.nimh.nih.gov nimhinfo@nih.gov
1-866-615-6464

NINDS National Institute of Neurological Disorders and Stroke
www.ninds.nih.gov braininfo@ninds.nih.gov
1-800-352-9424

NINR National Institute of Nursing Research
www.ninr.gov
301-496-0207

CENTERS & OFFICES

NLM National Library of Medicine
www.nlm.nih.gov
1-888 FIND NLM

CIT Center for Information Technology
www.cit.nih.gov
301-594-6248

CSR Center for Scientific Review
www.csr.nih.gov
301-435-1115

FIC Fogarty International Center
www.fic.nih.gov

NCCAM National Center for Complementary and Alternative Medicine
www.nccam.nih.gov
888-644-6226

NCMHD National Center on Minority Health and Health Disparities
www.ncmhd.nih.gov
301-402-1366

NCRR National Center for Research Resources
www.ncrr.nih.gov
301-435-0888

CC Warren G. Magnuson Clinical Center
www.cc.nih.gov

ORWH Office of Research on Women's Health
http://orwh.od.nih.gov
301-402-1770

OER Office of Extramural Research
www.grants.nih.gov/grants/oer.htm
301-435-0714

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